

0.30mL) in CH₂Cl₂ (10mL) at -78 °C was added dropwise a solution of trifluoromethanesulfonic anhydride (2eq, 3.00mmol, 0.50mL). The solution was allowed to warm to room temperature and further stirred for 1 hour. The mixture was quenched with cold water. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and evaporated under reduced pressure to afford the crude product 1-(3-fluorobenzyl)-1,2-dihydro-2-oxopyridin-4-yl trifluoromethanesulfonate as a viscous oil (0.90mmol, 0.41g, 90%). The crude product is used in the next step without further purification.

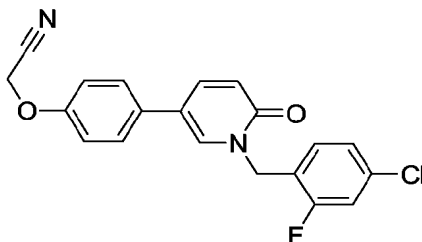
LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.34 min; MS *m/z* (CI) [MH]⁺ = 352.

Step 4 : 1-(3-Fluorobenzyl)-4-(4-methoxyphenyl)pyridin-2(1H)-one

According to Scheme 13 Method C: The title compound was prepared from 1-(3-fluorobenzyl)-1,2-dihydro-2-oxopyridin-4-yl trifluoromethanesulfonate (1eq, 0.28mmol, 0.10g) and 4-methoxyphenyl boronic acid (1.5eq, 0.43mmol, 65mg) according to the procedure described for Example 1 Step 3. The crude product was purified by flash chromatography on silica gel using cyclohexane/AcOEt 70/30 as eluent to afford the title compound (0.17mmol, 52mg, 59%) was obtained as a white solid.

M.p.: 114°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.18 min; MS *m/z* (CI) [MH]⁺ = 310; ¹H NMR (500MHz, DMSO-d₆) δ 3.80 (s, 3H), 5.11 (s, 2H), 6.62 (dd, J=2.1Hz and 7.2Hz, 1H), 6.66 (d, J=2.0Hz, 1H), 7.02 (d, J=8.9Hz, 2H), 7.09-7.17 (m, 3H), 7.36-7.42 (m, 1H), 7.70 (dd, J=2.1Hz and 6.8Hz, 2H), 7.85 (d, J=7.1Hz, 1H).

EXAMPLE 20 : 2-(4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-phenoxy)acetonitrile (Final Compound 6-46)



Step 1 : 1-(2-Fluoro-4-chlorobenzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

According to Scheme 3 Method A: The title compound was prepared from 1-(4-chloro-2-fluorobenzyl)-5-bromopyridin-2(1H)-one (1eq, 16.4mmol, 5.20g, Example 1 Step 2) and 4-methoxyphenylboronic acid (1.5eq, 25.0mmol, 3.80g) according to the procedure described for Example 1 Step 3. The crude product was purified by flash chromatography over silica gel using CH₂Cl₂/AcOEt 95/5 to 80/20 as eluent to afford 1-(2-fluoro-4-chlorobenzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (16.4mmol, 5.64g, 100%) as a white solid.

Rf = 0.29 (CH₂Cl₂/AcOEt 90/10); LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.58min; MS *m/z* (CI) [MH]⁺ = 344, 346.

Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1H)-one

According to Scheme 14 Step 1: BBr₃ (4eq, 65.6mmol, 6.56mL) was added to a solution of 1-(2-fluoro-4-chlorobenzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (16.4mmol, 5.64g) in CH₂Cl₂ at -50°C. The reaction mixture was stirred 1.5 hour at -40°C, overnight at room temperature then BBr₃ (20mL) was added at -30°C and the reaction mixture was stirred 4 hours at room temperature. The reaction mixture was cooled down to -40°C then MeOH (50mL) was added dropwise and the crude mixture was stirred at room temperature. After evaporation, the crude mixture was purified by silica gel chromatography (300g SiO₂) using CH₂Cl₂/MeOH 95/5 to afford 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1H)-one (14.9mmol, 4.80g, 83%) as an orange solid.

M.p.: 207°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.67min; MS *m/z* (CI) [MH]⁺ = 330; ¹H NMR (500MHz, CDCl₃) δ 5.16 (s, 2H), 6.47 (d, J=9.5Hz, 1H), 6.79 (d, J=8.7Hz, 2H), 7.15-7.20 (m, 1H), 7.25 (dd, J=2.1Hz and 8.7Hz, 1H), 7.34 (d, J=6.6Hz, 2H), 7.45 (dd, J=2.1Hz and 10.1Hz, 1H), 7.77 (dd, J=2.7Hz and 9.5Hz, 1H), 8.03 (d, J=2.7Hz, 1H), 9.51 (s, 1H).

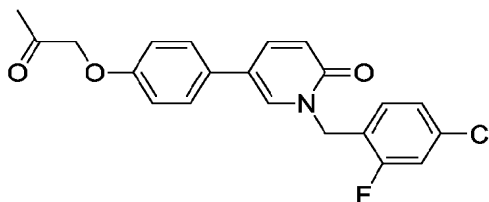
Step 3 : 2-(4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)-acetonitrile

According to Scheme 14 Method A: A suspension of 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1H)-one (1eq, 1.21mmol, 0.40g), K₂CO₃ (10eq, 12.1mmol,

1.68g) and 2-bromoacetonitrile (1eq, 1.21mmol, 0.15g) in acetonitrile (10mL) was heated in a microwave at 180°C during 5 min. The reaction mixture was filtered, the filtrate was concentrated and the resulting crude residue was dissolved in CH₂Cl₂. The organic phase was washed with water, dried over MgSO₄, filtered and evaporated. The crude oil was purified by flash chromatography over silica gel (AIT Flashsmart preppacked column 25g SiO₂) using CH₂Cl₂/MeOH 98/2 as eluent followed by trituration in acetonitrile to afford 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)acetonitrile (0.51mmol, 0.19g, 42%) as a white solid.

M.p.: 160°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.20min; MS *m/z* (CI) [MH]⁺ = 369, 371; ¹H NMR (300MHz, CDCl₃) δ 5.19 (s, 2H), 5.20 (s, 2H), 6.52 (d, J=9.5Hz, 1H), 7.11-7.16 (m, 2H), 7.18-7.23 (m, 1H), 7.27 (dd, J=2.0Hz and 8.4Hz, 1H), 7.46 (dd, J=2.0Hz and 10.1Hz, 1H), 7.55-7.60 (m, 2H), 7.86 (dd, J=2.7Hz and 9.5Hz, 1H), 8.16 (d, J=2.7Hz, 1H).

EXAMPLE 21 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-(2-oxopropoxy)phenyl)pyridin-2(1H)-one (Final Compound 6-40)

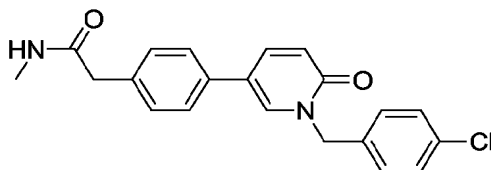


According to Scheme 14 Method A: A suspension of 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1H)-one (1eq, 0.61mmol, 0.20g, Example 20 Step 2), K₂CO₃ (10eq, 6.10mmol, 0.84g) and chloroacetone (4eq, 2.43mmol, 0.20mL) in THF (10mL) was heated in a microwave at 110°C during 30 min. After filtration and evaporation, the resulting crude oil was purified by flash chromatography over silica gel (AIT Flashsmart preppacked column 25g SiO₂) using CH₂Cl₂/AcOEt 80/20 then was washed with Et₂O and was dried to afford 1-(4-chloro-2-fluorobenzyl)-5-(4-(2-oxopropoxy)phenyl)pyridin-2(1H)-one (0.12mmol, 46mg, 20%) as a white solid.

M. p.: 127°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.02min; MS *m/z* (CI) [MH]⁺ = 386, 388; ¹H NMR (300MHz, CDCl₃) δ 2.16 (s, 3H), 4.83 (s, 2H), 5.18 (s, 2H), 6.50 (d, J=9.3Hz, 1H), 6.93-7.02 (m, 2H), 7.15-7.24 (m, 1H), 7.27 (dd, J=2.1Hz

and 8.7Hz, 1H), 7.42-7.51 (3H), 7.83 (dd, J=2.4Hz and 9.3Hz, 1H), 8.11 (d, J=2.4Hz, 1H).

EXAMPLE 22: 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)-N-methylacetamide (Final Compound 2-44)



Step 1 : 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetic acid

According to Scheme 3 Method A: The title compound was prepared according to
10 Example 2 Step 2, from 1-(4-chlorobenzyl)-5-bromopyridin-2(1H)-one (1eq, 0.67mmol, 0.20g, Example 2 Step 1) and 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid (1.5eq, 1.00mmol, 0.26g). Reaction conditions: 4.5 hours at 90°C. The reaction mixture was made acidic then extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue
15 was purified by chromatography over silicagel (AIT Flashsmart prepac column 25g SiO₂, AcOEt/MeOH 95/5), yielding the title compound (0.24g, 100%) as a white solid. LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.53min; MS *m/z* (CI) [MH]⁺ = 354, 356.

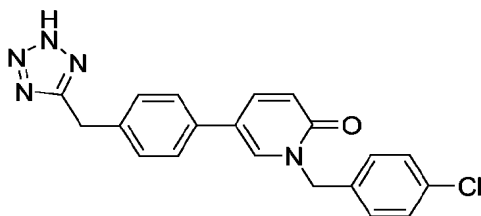
20 *Step 2 : 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)-N-methylacetamide*

Scheme 15 Method B: The title compound was prepared according to Example 14 Step 3, from 2-(4-(1-(4-chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetic acid (1eq, 0.10mmol, 50mg) and methylamine (2M in MeOH, 0.10mmol, 0.07mL), then
25 purified by chromatography over silicagel (AIT Flashsmart prepac column 10g SiO₂, CH₂Cl₂/AcOEt 50/50), yielding the title compound (0.07mmol, 34mg, 66%) as a white solid.

M.p.: 183°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.32min; MS *m/z* (CI) [MH]⁺ = 367, 369; ¹H NMR (300 MHz, DMSO-d₆) δ 2.56 (d, J=4.6Hz, 3H), 3.36

(s, 2H), 5.15 (s, 2H), 6.52 (d, J=9.5Hz, 1H), 7.29 (d, J=8.2Hz, 2H), 7.33-7.45 (4H), 7.49 (d, J=8.2Hz, 2H), 7.83 (dd, J= J=2.6Hz, 9.45Hz, 1H), 7.92-8.01 (m, 1H), 8.24 (d, J=2.6Hz, 1H).

5 EXAMPLE 23 : 5-(4-((2H-Tetrazol-5-yl)methyl)phenyl)-1-(4-chlorobenzyl)pyridin-2(1H)-one (Final Compound 2-51)



Step 1 : 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetonitrile

10 According to Scheme 3 Method A: The title compound was synthesized as described in Example 2 Step 2 using 4-(cyanomethyl)phenyl boronic acid (1.5eq, 0.50mmol, 80.9mg) and 1-(4-chlorobenzyl)-5-bromopyridin-2(1H)-one (1eq, 0.33mmol, 0.10g, Example 2 Step 1) as substrates. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepac column 25g SiO₂) using
15 CH₂Cl₂/AcOEt to afford 2-(4-(1-(4-chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetonitrile as a yellow solid (0.33mmol, 110mg, 98%).

M.p.: 172°C; LC (XTerra RP18, 3.5μm, 3.0x50mm Column): RT = 4.18 min, MS *m/z* (CI) [MH]⁺ = 335, 337.

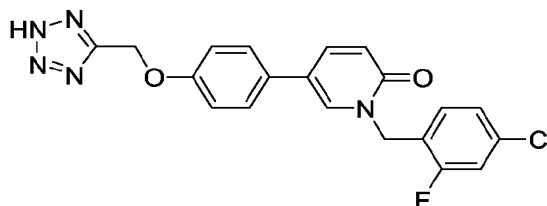
20 *Step 2 : 5-(4-((2H-Tetrazol-5-yl)methyl)phenyl)-1-(4-chlorobenzyl)pyridin-2(1H)-one*

According to Scheme 15 Method D: 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetonitrile (1eq, 0.24mmol, 0.08g) was heated at 110°C under nitrogen overnight with dibutyltin oxide (0.22eq, 0.05mmol, 0.01g) and azidotrimethylsilane (6.0eq, 1.43mmol, 0.19mL) in toluene (4mL). The suspension was
25 filtered and the filtrate concentrated under vacuo. The crude product was purified by chromatography on silica gel using MeOH/AcOEt 20/80 as eluent and recrystallised in diisopropyl ether to afford the title compound as a white solid (0.09mmol, 35mg, 39%).

M.p.: 231°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.56 min; MS *m/z* (CI) [MH]⁺ = 376, 378; ¹H NMR (500MHz, DMSO-d₆) δ 3.99 (s, 2H), 5.13 (s, 2H),

6.48 (d, J= 9.5Hz, 1H), 7.25 (d, J=8.4Hz, 2H), 7.35-7.40 (4H), 7.42 (d, J=8.4Hz, 2H), 7.80 (dd, J=2.7Hz and 9.5Hz, 1H), 8.21 (d, J=2.5Hz, 1H).

EXAMPLE 24 : 5-(4-((2H-Tetrazol-5-yl)methoxy)phenyl)-1-(4-chloro-2-fluorobenzyl)pyridin-2(1H)-one (Final Compound 6-65)

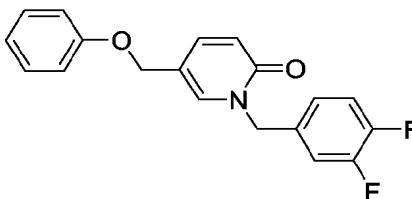


According to Scheme 15 Method D: The title compound was prepared from 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)acetonitrile (1eq, 0.35mmol, 0.13g, Example 20 Step 3) according to the procedure described for Example 23 Step 2. The crude product was purified by silica gel chromatography (AIT Flashsmart prepac column 10g SiO₂) using CH₂Cl₂/MeOH 95/5 as eluent followed by trituration in Et₂O to afford 5-(4-((2H-tetrazol-5-yl)methoxy)phenyl)-1-(4-chloro-2-fluorobenzyl)pyridin-2(1H)-one (85μmol, 35mg, 24%) as a white solid.

M.p.: 197°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.57min; MS *m/z* (CI) [MH]⁺= 412, 414; ¹H NMR (300MHz, CDCl₃) δ 3.00-3.60 (br. s, 1H), 5.18 (s, 2H), 5.35 (s, 2H), 6.50 (d, J=9.5Hz, 1H), 7.11-7.17 (m, 2H), 7.18-7.23 (m, 1H), 7.27 (dd, J=2.0Hz and 8.4Hz, 1H), 7.45 (dd, J=2.0Hz and 10.2Hz, 1H), 7.47-7.60 (m, 2H), 7.84 (dd, J=2.7Hz and 9.5Hz, 1H), 8.13 (d, J=2.7Hz, 1H).

20

EXAMPLE 25 : 1-(3,4-Difluorobenzyl)-5-(phenoxyethyl)pyridin-2(1H)-one (Final Compound 16-03)



Step 1 : (6-Methoxypyridin-3-yl)methanol

According to Scheme 16 Method A: A solution of 6-methoxynicotinaldehyde (1eq, 2.19mmol, 0.30g) and LiAlH₄ (0.5eq, 1.05mmol, 0.04g) in THF (10mL) was stirred for 30 min. at 0°C and overnight at room temperature. After the addition of AcOEt, the reaction mixture was diluted with water. The organic layer was washed with saturated NH₄Cl solution, dried over Na₂SO₄, filtered and evaporated. The resulting crude residue was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO₂) using CH₂Cl₂/AcOEt 80/20 to afford (6-methoxypyridin-3-yl)methanol (1.80mmol, 0.26g, 90%) as a pale oil.

10 LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 1.86min; MS *m/z* (CI) [MH]⁺= 140.

Step 2 : 2-Methoxy-5-(phenoxymethyl)pyridine

According to Scheme 16 Method A: Phenol (1.5eq, 2.80mmol, 0.26g), PPh₃ (2eq, 3.70mmol, 1.20g) and DEAD (2eq, 3.70mmol, 1.60g) were added to a solution of (6-methoxypyridin-3-yl)methanol (1eq, 1.87mmol, 0.26g) in THF (6mL). The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the reaction mixture was diluted with water. The organic layer was washed with saturated NaHCO₃ solution, dried over Na₂SO₄, filtered and evaporated. The resulting crude residue was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO₂) using cyclohexane/AcOEt 85/15 to afford 2-methoxy-5-(phenoxymethyl)pyridine (0.93mmol, 0.20g, 49%) as a pale oil.

20 LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.46min; MS *m/z* (CI) [MH]⁺= 216.

Step 3 : 1-(3,4-Difluorobenzyl)-5-(phenoxymethyl)pyridin-2(1H)-one

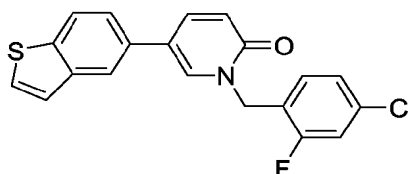
According to Scheme 16 Method A: The title compound was prepared from 2-methoxy-5-(phenoxymethyl)pyridine (1eq, 0.46mmol, 0.10g) and 4-(bromomethyl)-1,2-difluorobenzene (3eq, 1.39mmol, 0.18mL) according to the procedure described for Example 1 Step 2. Reaction conditions: under reflux for 3 days in DMF (5mL). The crude oil was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g SiO₂) using CH₂Cl₂/AcOEt 90/10 followed by recrystallization

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in diisopropyl ether to afford 1-(3,4-difluorobenzyl)-5-(phoxymethyl)pyridin-2(1*H*)-one (0.14mmol, 0.04g, 29%) as a white solid.

M.p.: 89°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.29min; MS *m/z* (CI) [MH]⁺ = 328; ¹H NMR (500MHz, DMSO-d₆) δ 4.80 (s, 2H), 5.06 (s, 2H), 6.45 (d, J=9.3Hz, 1H), 6.91-6.96 (m, 1H), 6.96-6.99 (m, 2H), 7.12-7.17 (m, 1H), 7.25-7.30 (m, 2H), 7.36-7.43 (m, 2H), 7.53 (dd, J=2.5Hz and 9.3Hz, 1H), 7.99 (d, J=2.3Hz, 1H).

EXAMPLE 26 : 1-(4-Chloro-2-fluorobenzyl)-5-(benzo[*b*]thiophen-5-yl)pyridin-2(1*H*)-one (Final Compound 6-69)



*Step 1 : 1-(4-Chloro-2-fluorobenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one*

According to Scheme 17 Step 1: To a solution of 1-(4-chloro-2-fluorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 1.26mmol, 0.40g, Example 1 Step 2) in degazed dioxane (20mL) was added under nitrogen 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.3eq, 1.64mmol, 0.42g), PdCl₂(dppf)₂ (0.03eq, 38µmol, 28mg), dppf (0.06eq, 76µmol, 42mg) and KOAc (3eq, 3.79mmol, 0.37g). The reaction mixture was stirred at 80°C for 4 hours, was quenched with water and the aqueous phase was extracted with AcOEt. The organic phase was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO₂) using CH₂Cl₂/AcOEt 90/10 as eluent to afford 1-(4-chloro-2-fluorobenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (0.74mmol, 0.27g, 59%) as a pale oil.

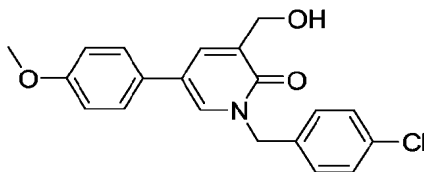
LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.03min; MS *m/z* (CI) [MH]⁺ = 364, 366.

Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(benzo[b]thiophen-5-yl)pyridin-2(1H)-one

According to Scheme 17 Step 2: The title compound was prepared from 1-(4-chloro-2-fluorobenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (1eq, 1.26mmol, 0.40g) and 5-bromobenzo[b]thiophene (1.5eq, 0.29mmol, 0.06g) according to the procedure described for Example 1 Step 2. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepac column 25g SiO₂) using CH₂Cl₂/AcOEt 90/10 and by crystallization with diisopropyl ether/pentane to afford the title compound (17μmol, 6.4mg, 9%) as a white solid.

M.p.: 110°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 5.03min; MS *m/z* (CI) [MH]⁺ = 370, 372; ¹H NMR (500MHz, DMSO-d₆) δ 5.21 (s, 2H), 6.55 (d, J=9.5Hz, 1H), 7.19-7.24 (m, 1H), 7.26-7.30 (m, 1H), 7.43-7.49 (m, 2H), 7.57 (dd, J=1.8Hz and 8.6Hz, 1H), 7.80 (d, J=5.4Hz, 1H), 7.95 (dd, J=2.7Hz and 9.4Hz, 1H), 8.05 (d, J=8.4Hz, 1H), 8.07 (d, J=1.6Hz, 1H), 8.28 (d, J=2.3Hz, 1H).

Example 27 : 1-(4-Chlorobenzyl)-3-(hydroxymethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (Final Compound 9-08)



Step 1 : Methyl 1-(4-chlorobenzyl)-5-bromo-2-oxo-1,2-dihydropyridine-3-carboxylate

According to Scheme 1 Step 2: The title compound was prepared from methyl 5-bromo-2-oxo-1,2-dihydropyridine-3-carboxylate (1eq, 10.0mmol, 3.00g) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 20.0mmol, 4.00g) according to the procedure described for Example 1 Step 2. Reaction conditions: 3 hours at 50°C in THF/DMF (2:1, 300mL). The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepac column 130g SiO₂) using CH₂Cl₂/AcOEt 85/15 as the eluent and recrystallized from Et₂O to afford the title compound (9.00mmol, 4.17g, 90%) as a white solid.

LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.05min; MS *m/z* (CI) [MH]⁺ = 357, 359.

Step 2 : Methyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

According to Scheme 3 Method A: The title compound was prepared from methyl 1-(4-chlorobenzyl)-5-bromo-2-oxo-1,2-dihydropyridine-3-carboxylate (1eq, 7.00mmol, 2.50g) and 4-methoxyphenyl boronic acid (1.5eq, 11.0mmol, 1.60g) according to the procedure described for Example 1 Step 3. Reaction conditions: 4 hours at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart preppacked column 80g SiO₂) using CH₂Cl₂/AcOEt 80/20 and by recrystallization with Et₂O/pentane to afford methyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (5.74mmol, 2.22g, 82%) as a beige solid.

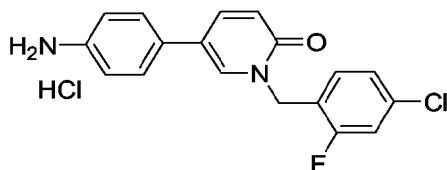
LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.38min; MS *m/z* (CI) [MH]⁺ = 384, 386.

Step 3 : 1-(4-Chlorobenzyl)-3-(hydroxymethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

According to Scheme 18: To a solution of methyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (1eq, 0.52mmol, 0.20g) in Et₂O (7mL) at -78°C was added DIBAL (3eq, 1.60mmol, 1.11g). The reaction was stirred at -78°C for 30 minutes and 0°C for 1 hour. The reaction was then allowed to warm to room temperature and quenched with saturated aqueous NH₄Cl solution. The aqueous phase was extracted 3 times with AcOEt and the combined organic fractions were washed twice with water, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart preppacked 50g column SiO₂) using CH₂Cl₂/AcOEt 80/20 as eluent which was then recrystallized from pentane/Et₂O to afford the title compound (0.04mmol, 16.0mg, 9%) as a beige solid.

M.p.: 128°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.98min; MS *m/z* (CI) [MH]⁺ = 356, 358; ¹H NMR (300MHz, DMSO-d₆) δ 3.77 (s, 3H), 4.37 (d, J=5.8Hz, 2H), 5.12-5.19 (3H), 7.00 (d, J=8.9Hz, 2H), 7.35-7.43 (m, 4H), 7.44-7.52 (m, 2H), 7.72-7.76 (m, 1H), 8.07-8.10 (m, 1H).

EXAMPLE 28 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-aminophenyl)pyridin-2(1H)-one hydrochloride (Final Compound 6-23)



5 Step 1 : *tert*-Butyl 4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenylcarbamate

According to Scheme 19 Step 1: The title compound was prepared from 1-(4-chloro-2-fluorobenzyl)-5-bromopyridin-2(1H)-one (1eq, 2.81mmol, 0.89g, Example 1 Step 2) and 4-(*tert*-butoxycarbonyl)aminophenylboronic acid (1.5eq, 4.20mmol, 1.00g) according to the procedure described for Example 1 Step 3. Reaction conditions: 2 hours at 80°C. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 50g SiO₂, CH₂Cl₂/AcOEt 90/10). The resulting brown solid was washed twice with acetonitrile to afford *tert*-butyl 4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenylcarbamate (2.11mmol, 0.90g, 75%) as a beige solid.

M.p.: 208°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.82min; MS *m/z* (CI) [MH]⁺ = 429, 431.

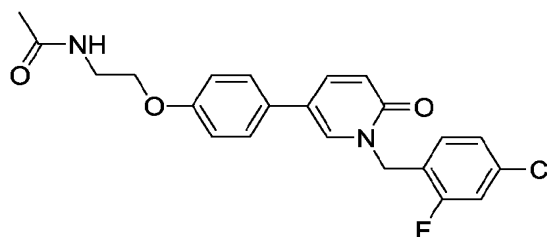
20 Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-aminophenyl)pyridin-2(1H)-one hydrochloride

According to Scheme 19 Step 2: HCl/dioxane (10eq, 4M, 5.00mL) was added to a solution of *tert*-butyl 4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenylcarbamate (1eq, 2.00mmol, 1.00g) in MeOH (20mL) at 0°C. The reaction was stirred for 2 days at 80°C, then the solvent was concentrated and Et₂O was added. The solid was filtered and dried to yield 1-(4-chloro-2-fluorobenzyl)-5-(4-aminophenyl)pyridin-2(1H)-one hydrochloride (1.78mmol, 0.76g, 89%) as a beige solid.

M.p.: 266°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.18min; MS *m/z* (CI) [MH]⁺ = 329, 331; ¹H NMR (300MHz, DMSO-d₆) δ 3.10-3.70 (br s, 3H), 5.19 (s,

2H), 6.53 (d, J=9.5Hz, 1H), 7.16-7.24 (m, 1H), 7.24-7.37 (3H), 7.46 (dd, J=1.8Hz and 10.2Hz, 1H), 7.63 (dd, J=8.2Hz, 2H), 7.87 (dd, J=2.6Hz and 9.5Hz, 1H), 8.23 (s, 1H).

5 **EXAMPLE 29 : *N*-(2-(4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethyl)acetamide (Final Compound 6-53)**



10 *Step 1 : tert-Butyl 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethylcarbamate*

The title compound was prepared from 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1H)-one (1eq, 0.60mmol, 0.20g, Example 20 Step 2) and *tert*-butyl 2-hydroxyethylcarbamate (1.5eq, 0.90mmol, 0.10g) according to the procedure described for Example 25 Step 2. The crude product was purified by
15 crystallization in pentane/Et₂O followed by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO₂, CH₂Cl₂/AcOEt 80/20) to afford *tert*-butyl 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethylcarbamate (0.40mmol, 0.19g, 66%) as a yellow oil.

20 LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.73min; MS *m/z* (CI) [MH]⁺= 473, 475.

Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-(2-aminoethoxy)phenyl)pyridin-2(1H)-one
According to Scheme 19 Step 2: The title compound was prepared from *tert*-butyl 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethylcarbamate
25 (1eq, 0.40mmol, 0.19g) according to the procedure described for Example 28 Step 2. Reaction conditions: room temperature overnight. After trituration with Et₂O, 1-(4-chloro-2-fluorobenzyl)-5-(4-(2-aminoethoxy)phenyl)pyridin-2(1H)-one (0.40mmol, 0.16g, 100%) was obtained as a white solid.

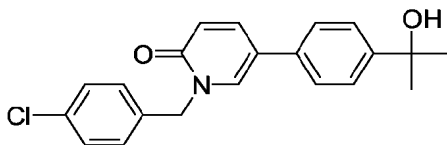
M.p.: 226°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 2.63min; MS *m/z* (CI) [MH]⁺ = 373, 375.

Step 3 : N-(2-(4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethyl)acetamide

According to Scheme 19 Step 3: To a solution of 1-(4-chloro-2-fluorobenzyl)-5-(4-(2-aminoethoxy)phenyl)pyridin-2(1*H*)-one (1eq, 0.18mmol, 0.07g) in CH₂Cl₂ (5mL) at 0°C were added Et₃N (6eq, 1.10mmol, 0.15mL) and 30 min. later acetyl chloride (1.5eq, 0.27mmol, 19µL) and. The reaction mixture was stirred 1 hour at room temperature. The reaction mixture was quenched with water and extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and evaporated. The crude product was purified by silica gel chromatography (AIT Flashsmart prepac column 25g SiO₂, CH₂Cl₂/AcOEt 70/30) to afford *N*-(2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethyl)acetamide (0.08mmol, 0.04g, 47%) as a white solid.

M.p.: 153°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.51min; MS *m/z* (CI) [MH]⁺ = 415, 417; ¹H NMR (300MHz, DMSO-*d*⁶) δ 3.16 (s, 3H), 3.99 (t, J=5.6Hz, 2H), 5.18 (s, 2H), 5.75 (s, 1H), 6.51 (d, J=9.5Hz, 1H), 7.00 (d, J=8.7Hz, 2H), 7.15-7.23 (m, 1H), 7.23-7.29 (m, 1H), 7.43-7.53 (m, 3H), 7.84 (dd, J=2.8Hz and 9.5Hz, 1H), 8.09-8.20 (m, 1H).

EXAPLE 30 : 1-(4-Chlorobenzyl)-5-(4-(2-hydroxypropan-2-yl)phenyl)pyridin-2(1*H*)-one (Final Compound 2-15)



*Step 1 : 1-(4-Chlorobenzyl)-5-(4-acetylphenyl)pyridin-2(1*H*)-one*

According to Scheme 3 Method A: The title compound was prepared from 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (Example 2 Step 1) and 4-acetylphenylboronic acid according to the procedure described for Example 2 Step 2. Reaction conditions: 4 hours at 80°C. The crude product was purified by silica gel

chromatography (AIT Flashsmart prepac column 25g SiO₂) using CH₂Cl₂/AcOEt 50/50 as eluent to afford 1-(4-chlorobenzyl)-5-(4-acetylphenyl)pyridin-2(1H)-one (0.29mmol, 0.10g, 86%) as a yellow solid.

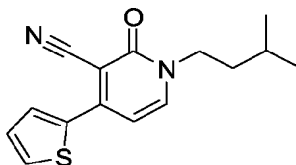
M.p.: 162°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.21min; MS *m/z* (CI) [MH]⁺ = 338, 340; ¹H NMR (500MHz, DMSO-d₆) δ 2.58 (s, 3H), 5.17 (s, 2H), 6.55 (d, J=9.4Hz, 1H), 7.37-7.42 (4H), 7.74 (d, J=2.6Hz, 2H), 7.95 (dd, J=2.6Hz and 9.4Hz, 1H), 7.99 (d, J=8.6Hz, 2H), 8.45 (d, J=2.6Hz, 1H).

Step 2 : 1-(4-Chlorobenzyl)-5-(4-(2-hydroxypropan-2-yl)phenyl)pyridin-2(1H)-one

According to Scheme 20: To a solution of 1-(4-chlorobenzyl)-5-(4-acetylphenyl)pyridin-2(1H)-one (1eq, 0.20mmol, 80mg) in THF (5mL) at -50°C was added a solution of methyl magnesium bromide (3M, 1.3eq, 0.30mmol, 0.04g) and the reaction stirred at -50°C for 1 hour. The reaction was quenched at -78°C with saturated aqueous NH₄Cl. The reaction was allowed to warm to room temperature and diluted with AcOEt and the organic phase extracted (x3). The combined organic fractions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepac column 25g SiO₂) using CH₂Cl₂/AcOEt 80/20 and was recrystallized from pentane/Et₂O to afford 1-(4-chlorobenzyl)-5-(4-(2-hydroxypropan-2-yl)phenyl)pyridin-2(1H)-one (0.08mmol, 30mg, 36%) as a white solid.

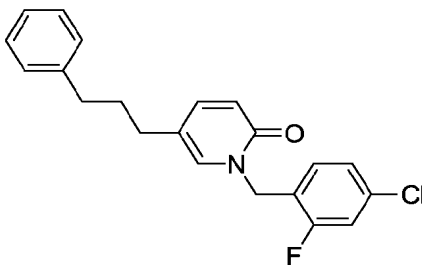
M.p.: 157°C. LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.86min; MS *m/z* (CI) [MH]⁺ = 354, 356. ¹H NMR (300MHz, DMSO-d₆) δ 1.42 (s, 6H), 5.05 (s, 1H), 5.15 (s, 2H), 6.52 (d, J=9.7Hz, 1H), 7.32-7.43 (m, 4H), 7.43-7.52 (m, 3H), 7.84 (dd, J=1.8Hz, 9.5Hz, 1H), 8.22 (d, J=1.8Hz, 1H).

EXAMPLE 31 : 1,2-Dihydro-1-isopentyl-2-oxo-4-(thiophen-2-yl)pyridine-3-carbonitrile (Final Compound 10-28)



According to Scheme 21: The title compound was prepared according to Example 1 Step 2 from 1,2-dihydro-2-oxo-4-(thiophen-2-yl)pyridine-3-carbonitrile (1eq, 0.50mmol, 0.10g) and 1-bromo-3-methylbutane (1.5eq, 0.70mmol, 0.10g). Reaction conditions: 17 hours at 60°C in acetonitrile (10mL). The crude product was purified by chromatography over silicagel (AIT Flashsmart prepac column SiO₂, cyclohexane/AcOEt 80/20) and recrystallized in pentane/Et₂O yielding the title compound (88mg, 0.30mmol, 65%) as a yellow solid. M.p.: 123°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.29min; MS *m/z* (CI) [MH]⁺ = 273; ¹H NMR (300 MHz, DMSO-d₆) δ 0.92 (d, J=5.6Hz, 6H), 1.48-1.63 (m, 3H), 3.90-4.02 (m, 2H), 6.72 (d, J=7.2Hz, 1H), 7.32 (d, J=8.4Hz, 1H), 7.96-8.04 (m, 2H), 8.08 (d, J=7.2Hz, 1H).

EXAMPLE 32 : 1-(4-Chloro-2-fluorobenzyl)-5-(3-phenylpropyl)pyridin-2(1H)-one (Final Compound 7-08)



Step 1 : 2-Methoxy-5-(3-phenylpropyl)pyridine

According to Scheme 22 Method A: To a solution of 5-bromo-2-methoxypyridine (1eq, 2.70mmol, 0.50g) in THF (4.4mL) at -78°C under nitrogen was added dropwise n-butyl lithium (1eq, 2.5M in hexanes, 2.70mmol, 1.10mL). The reaction mixture was stirred at -78°C for 30 min. and 1-(3-bromopropyl)benzene (1eq, 2.70mmol, 0.40mL) in solution in THF (1mL) was added dropwise. The reaction mixture was stirred at -78°C for 30 min. and then allowed to warm to room temperature for 1 hour. The reaction was quenched at 0°C with water and extracted with Et₂O. The organic phase was dried over Na₂SO₄, filtered and solvent was removed under reduced pressure leaving an orange oil. This residue was purified by flash chromatography over silicagel (AIT Flashsmart prepac column SiO₂, cyclohexane/AcOEt 97.5/2.5), yielding the title compound (0.46mmol, 0.10g, 17%) as a colorless semi-solid.

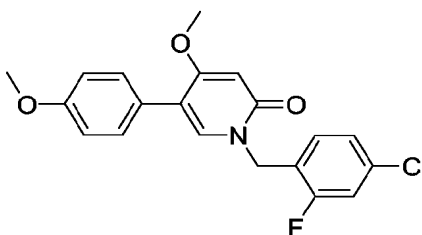
LC (XTerra RP₁₈, 3.5 μ m, 3.0x50mm Column): RT = 5.08min; MS *m/z* (CI) [MH]⁺= 228.

Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(3-phenylpropyl)pyridin-2(1H)-one

- 5 According to Scheme 22 Step 2: The title compound was prepared according to Example 6 Step 2, from 2-methoxy-5-(3-phenylpropyl)pyridine (1eq, 0.44mmol, 0.10g) and 1-(bromomethyl)-4-chloro-2-fluorobenzene (2eq, 0.88mmol, 0.20g). Reaction conditions: overnight at 90°C. The residue was purified by flash chromatography over silicagel (AIT Flashsmart prepacked column SiO₂, cyclohexane/AcOEt 70/30) yielding
- 10 the title compound (75mg, 0.21mmol, 48%) as a yellow oil.

LC (XTerra RP₁₈, 3.5 μ m, 3.0x50mm Column): RT = 5.07min; MS *m/z* (CI) [MH]⁺= 356, 358; ¹H NMR (300 MHz, CDCl₃) δ 1.76-1.93 (m, 2H), 2.30-2.46 (m, 2H), 2.52-2.70 (m, 2H), 5.09 (s, 2H), 6.54 (d, J=9.2Hz, 1H), 7.04-7.35 (9H), 7.35-7.50 (m, 1H).

- 15 **EXAMPLE 33 : 1-(4-Chloro-2-fluorobenzyl)-4-methoxy-5-(4-methoxyphenyl)pyridin-2(1H)-one (Final Compound 9-18)**



Step 1 : 2,4-Dimethoxypyridine

- 20 According to Scheme 23 Step 1: To a solution of sodium methoxide (30% in MeOH, 2eq, 35mmol) was added 2-chloro-4-methoxypyridine (1eq, 17.0mmol, 2.50g). The reaction was refluxed overnight. The reaction was allowed to cool, poured onto water (10mL) and extracted with CH₂Cl₂ (3x10mL). The combined organic fractions were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford 2,4-
- 25 dimethoxypyridine (10.1mmol, 1.40g, 58%) as a colorless oil. The crude product was reacted on.

LC (XTerra RP₁₈, 3.5 μ m, 3.0x50mm Column): RT = 1.40min; MS *m/z* (CI) [MH]⁺= 140.

Step 2 : 5-Bromo-2,4-dimethoxypyridine

According to Scheme 23 Step 2: To a solution of KOH (0.5eq, 0.8mmol, 40mg) in water (75mL) was added 2,4-dimethoxypyridine (1eq, 2.00mmol, 0.21g) followed by the dropwise addition of Br₂ (1eq, 2.00mmol, 0.20g) in 1M aqueous KBr solution (75mL). The reaction was stirred at room temperature for 5 hours and then poured onto water (10mL) and extracted with CH₂Cl₂ (3x10mL). The combined organic fractions were dried (MgSO₄), filtered and concentrated under reduced pressure to afford 5-bromo-2,4-dimethoxypyridine (1.40mmol, 0.30g, 70%) as a colorless oil. The crude product was reacted on.

LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.92min; MS *m/z* (CI) [MH]⁺= 219, 221.

Step 3 : 2,4-Dimethoxy-5-(4-methoxyphenyl)pyridine

According to Scheme 23 Step 3: The title compound was prepared from 5-bromo-2,4-dimethoxypyridine (1eq, 1.40mmol, 0.30g) and 4-methoxyphenylboronic acid (1.5eq, 2.10mmol, 0.32g) according to the procedure described for Example 1 Step 3. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepac column 25g SiO₂) using CH₂Cl₂/MeOH 98/2 to afford 2,4-dimethoxy-5-(4-methoxyphenyl)pyridine (1.39mmol, 0.34g, 99%) as a brown oil.

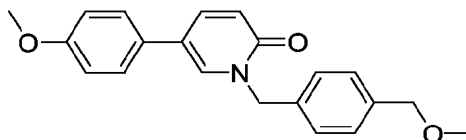
LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.85min; MS *m/z* (CI) [MH]⁺= 246, 248.

Step 4 : 1-(4-Chloro-2-fluorobenzyl)-4-methoxy-5-(4-methoxyphenyl)pyridin-2(1H)-one

According to Scheme 23 Step 4: The title compound was prepared from 2,4-dimethoxy-5-(4-methoxyphenyl)pyridine (1eq, 0.20mmol, 0.05g) and 4-chlorobenzyl-2-fluorobenzyl bromide (1.5eq, 0.30mmol, 68mg) according to the procedure described for Example 6 Step 2. Reaction conditions: 80°C for 2 days. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepac column 25g SiO₂) using CH₂Cl₂/MeOH 98/2 to afford 1-(4-chloro-2-fluorobenzyl)-4-methoxy-5-(4-methoxyphenyl)pyridin-2(1H)-one (0.10mmol, 36mg, 48%).

LC (XTerra RP₁₈, 3.5 μ m, 3.0x50mm Column): RT = 4.62min; MS *m/z* (CI) [MH]⁺= 374, 376; ¹H NMR (300 MHz, CDCl₃) δ 3.78 (s, 3H), 3.82 (s, 3H), 5.11 (s, 2H), 5.99 (s, 1H), 6.88-6.95 (m, 2H), 7.08-7.15 (m, 2H), 7.20-7.30 (m, 3H), 7.40-7.50 (m, 1H).

5 **EXAMPLE 34 : 1-(4-(Methoxymethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (Final Compound 4-25)**



Step 1 : 2-Methoxy-5-(4-methoxyphenyl)pyridine

- 10 According to Scheme 4 Method B: The title compound was prepared according to Example 1 Step 3 from 5-bromo-2-methoxypyridine (12.1mmol, 2.30g) and 4-methoxyphenylboronic acid (18.2mmol, 2.76g), then purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g SiO₂, CH₂Cl₂/MeOH 100/0 to 95/5), yielding the title compound (1.60g, 61%).
- 15 LC (XTerra RP₁₈, 3.5 μ m, 3.0x50mm Column): RT = 3.03min; MS *m/z* (CI) [MH]⁺= 216.

Step 2 : 1-(4-(Hydroxymethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

- According to Scheme 4 Step 1: The title compound was prepared according to Example
- 20 6 Step 2, from 2-methoxy-5-(4-methoxyphenyl)pyridine (1eq, 4.60mmol, 1.00g) and (4-(bromomethyl)phenyl)methanol (1.1eq, 5.10mmol 1.00g). Reaction conditions: 5 hours at 70°C and room temperature overnight. The residue was triturated with pentane, yielding the title compound (3.70mmol, 1.20g, 80%).
- LC (XTerra RP₁₈, 3.5 μ m, 3.0x50mm Column): RT = 3.23min; MS *m/z* (CI) [MH]⁺=
- 25 322.

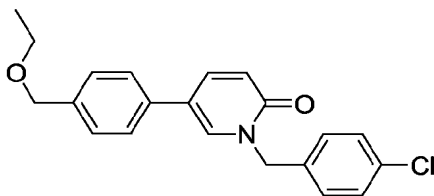
Step 3 : 1-(4-(Methoxymethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

- According to Scheme 24 Step 3: A mixture of 1-(4-(hydroxymethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (1eq, 0.25mmol, 0.08g), NaH (55%, 1.5eq,
- 30 0.37mmol, 18mg) and iodomethane (3eq, 0.75mmol, 0.11g) in DMF (2mL) was stirred

at room temperature overnight. The crude was diluted with AcOEt. The organic layer was washed with water, dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 5g SiO₂, CH₂Cl₂/MeOH 99/1), yielding the title compound (0.14mmol, 46mg, 55%) as white solid.

M.p.: 72°C; LC (Zorbax C₁₈, 3.5µm, 4.6x50mm Column): RT = 3.92min; MS *m/z* (CI) [MH]⁺ = 336; ¹H NMR (300 MHz, CDCl₃) δ 3.25 (s, 3H), 3.77 (s, 3H), 4.36 (s, 2H), 5.15 (s, 2H), 6.50 (d, J=9.3Hz, 1H), 6.98 (d, J=9.0Hz, 2H), 7.25-7.39 (m, 4H), 7.49 (d, J=9.0Hz, 2H), 7.80 (dd, J=2.7Hz and 9.6Hz, 1H), 8.15 (d, J=2.7Hz, 1H).

EXAMPLE 35 : 1-(4-Chlorobenzyl)-5-(4-(ethoxymethyl)phenyl)pyridin-2(1H)-one (Final Compound 2-25)



Step 1 : 1-(4-Chlorobenzyl)-5-(4-(hydroxymethyl)phenyl)pyridin-2(1H)-one

According to Scheme 25 Step 2: The title compound was prepared from 1-(4-chlorobenzyl)-5-bromopyridin-2(1H)-one (1eq, 3.30mmol, 1.00g, Example 2 Step 1) and 4-(hydroxymethyl)phenylboronic acid (1.5eq, 5.00mmol, 0.76g) according to the procedure described for Example 1 Step 3. Reaction conditions: overnight at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 70g SiO₂) using CH₂Cl₂/MeOH 98/2 as the eluent to afford 1-(4-chlorobenzyl)-5-(4-(hydroxymethyl)phenyl)pyridin-2(1H)-one (1.72mmol, 0.62g, 52%) as a brown oil LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.47min; MS *m/z* (CI) [MH]⁺ = 326, 328.

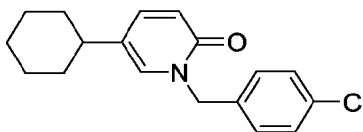
Step 2 : 1-(4-Chlorobenzyl)-5-(4-(ethoxymethyl)phenyl)pyridin-2(1H)-one

According to Scheme 25 Method A: The title compound was prepared from 1-(4-chlorobenzyl)-5-(4-(hydroxymethyl)phenyl)pyridin-2(1H)-one (1eq, 2.50mmol, 0.80g) and iodoethane (3eq, 7.40mmol, 1.10g) according to the procedure described for

Example 34 Step 3. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart preppacked column 5g SiO₂) using CH₂Cl₂/MeOH 99/1 as eluent to afford 1-(4-chlorobenzyl)-5-(4-(ethoxymethyl)phenyl)pyridin-2(1*H*)-one (1.02mmol, 0.36g, 41%) as a yellow solid.

- 5 M.p.: 109°C; LC (Zorbax C₁₈, 3.5μm, 4.6x50mm Column): RT = 4.62min; MS *m/z* (CI) [MH]⁺ = 354, 356; ¹H NMR (300 MHz, DMSO-d₆) δ 1.15 (t, J=6.9Hz, 3H), 3.47 (q, J=6.9Hz, 2H), 4.45 (s, 2H), 5.16 (s, 2H), 6.53 (d, J=9.6Hz, 1H), 7.32-7.40 (4H), 7.55 (d, J=8.4Hz, 2H), 7.85 (dd, J=2.7Hz and 9.3Hz, 1H), 8.28 (d, J=2.7Hz, 1H).

10 **EXAMPLE 36 : 1-(4-Chlorobenzyl)-5-cyclohexylpyridin-2(1*H*)-one (Final Compound 2-01)**



Step 1 : 1-(6-Methoxypyridin-3-yl)cyclohexanol

- 15 According to Scheme 26 Step 1: To a stirred solution of 4-bromo-2-methoxypyridine (1eq, 5.30mmol, 1.00g) in anhydrous THF (30mL) at -78°C under nitrogen was added dropwise a solution of butyl lithium (1.3eq, 2.5M solution in hexane, 6.90mmol, 2.8mL). The reaction was then stirred at -78°C for 2 hours. Cyclohexanone (5eq, 27.0mmol, 2.8mL) was then added dropwise over 5 minutes. The reaction was stirred at
- 20 -78°C for two hours then allowed to warm to room temperature. The reaction was stirred for a further 16 hours then quenched with water. The reaction was evaporated *in vacuo*, redissolved in CH₂Cl₂ (100mL) and washed with brine (100mL). The organic phase was extracted, dried over MgSO₄, filtered and evaporated to leave a yellow oil.
- The oil was purified by column chromatography (AIT Flashsmart preppacked column
- 25 25g SiO₂, pure AcOEt), yielding the title compound (4.10mmol, 0.86g, 78%) as a colorless oil which solidified on standing.

LC (Zorbax C₁₈, 3.5μm, 4.6x50mm Column): RT = 3.33min; MS *m/z* (CI) [MH]⁺ = 208.

Step 2 : 5-Cyclohexenyl-2-methoxypyridine

According to Scheme 26 Step 2: The title compound was prepared from 1-(6-methoxypyridin-3-yl)cyclohexanol (1eq, 1.21mmol, 0.25g) and methanesulfonyl chloride (4eq, 4.82mmol, 0.37mL) according to the procedure described for Example 4
5 Step 1. The crude residue was purified by chromatography over silicagel (AIT Flashsmart prepaced column 10g SiO₂, AcOEt/pentane 30/10 to pure AcOEt), yielding the title compound (0.76mmol, 0.14g, 63%) as a colorless oil.

LC (Zorbax C₁₈, 3.5µm, 4.6x50mm Column): RT = 5.08min; MS *m/z* (CI) [MH]⁺= 190.

10

Step 3 : 5-Cyclohexyl-2-methoxypyridine

According to Scheme 26 Step 3: The title compound was prepared according to Example 19 Step 2, from 5-cyclohexenyl-2-methoxypyridine (1eq, 0.74mmol, 0.14g). Reaction conditions: 32 hours at room temperature. The residue was purified by
15 chromatography over silicagel (AIT Flashsmart prepaced column 10g SiO₂, CH₂Cl₂/AcOEt 95/5), yielding the title compound (0.33mmol, 63mg, 45%) as a colorless oil.

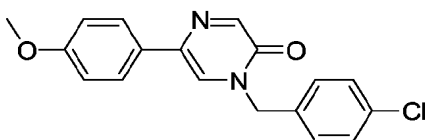
LC (Zorbax C₁₈, 3.5µm, 4.6x50mm Column): RT = 5.15min; MS *m/z* (CI) [MH]⁺= 192.

20 *Step 4 : 1-(4-Chlorobenzyl)-5-cyclohexylpyridin-2(1H)-one*

According to Scheme 26 Step 4: The title compound was prepared according to Example 6 Step 2, from 5-cyclohexyl-2-methoxypyridine (1eq, 0.30mmol, 57mg) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 0.44mmol, 92mg), then purified by chromatography over silicagel (AIT Flashsmart prepaced column 5g SiO₂,
25 CH₂Cl₂/MeOH 98/2) then recrystallized in pentane/diisopropyl ether, yielding the title compound (0.20mmol, 0.09g, 68%) as a beige solid.

M.p.: 72°C; LC (Zorbax C₁₈, 3.5µm, 4.6x50mm Column): RT = 5.07min; MS *m/z* (CI) [MH]⁺= 302, 304; ¹H NMR (300 MHz, CDCl₃) δ 1.07–1.43 (5H), 1.63–1.86 (5H), 2.13–2.28 (m, 1H), 5.08 (s, 2H), 6.58 (d, J=9.5Hz, 1H), 6.99 (d, J=2.6Hz, 1H), 7.20–
30 7.25 (m, 2H), 7.26–7.30 (m, 2H), 7.31–7.33 (m, 1H).

EXAMPLE 37 : 1-(4-Chlorobenzyl)-5-(4-methoxyphenyl)pyrazin-2(1H)-one (Final Compound 12-06)



5

Step 1 : 1-(4-Chlorobenzyl)-5-bromopyrazin-2(1H)-one

According to Scheme 27 Step 1: The title compound was prepared from 5-bromopyrazin-2(1H)-one (1eq, 2.86mmol, 0.50g) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 4.29mmol, 0.88g) according to the procedure described for
10 Example 1 Step 2. Reaction conditions: 3 hours at 70°C in acetonitrile. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g SiO₂) using pure AcOEt as eluent to afford 1-(4-chlorobenzyl)-5-bromopyrazin-2(1H)-one (2.48mmol, 0.74g, 87%) as a white solid.

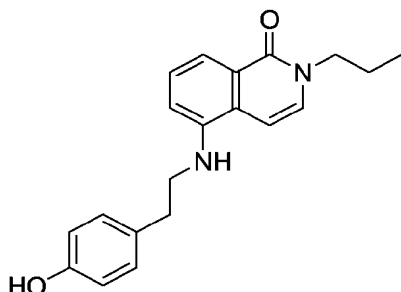
LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.91min; MS *m/z* (CI) [MH]⁺=
15 300, 302.

Step 2 : 1-(4-Chlorobenzyl)-5-(4-methoxyphenyl)pyrazin-2(1H)-one

According to Scheme 27 Step 2: The title compound was prepared from 1-(4-chlorobenzyl)-5-bromopyrazin-2(1H)-one (1eq, 0.67mmol, 0.20g) and 4-methoxyphenylboronic acid (1.5eq, 1.00mmol, 0.15g) according to the procedure
20 described for Example 1 Step 3. Reaction conditions: 1 hour at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 10g SiO₂) using CH₂Cl₂/MeOH (98/2) as the eluent to afford 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)pyrazin-2(1H)-one (0.47mmol, 0.15g, 71%) as a
25 beige solid.

M.p.: 133°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.41min; MS *m/z* (CI) [MH]⁺= 327, 329. ¹H NMR (300 MHz, DMSO-d₆) δ 3.78 (s, 3H), 5.12 (s, 2H), 7.00 (d, J=9.0Hz 2H), 7.40-7.50 (m, 4H), 7.77 (d, J=9.0Hz, 2H), 8.14 (s, 1H), 8.39 (s, 1H).

EXAMPLE 38 : 5-(4-Hydroxyphenethylamino)-2-propylisoquinolin-1(2H)-one
(Final Compound 13-05)



5 *Step 1 : 5-Chloroisoquinoline N-oxide*

According to Scheme 28 Step 1: A solution of MCPBA (1.9, 15.0mmol, 3.6g) and 5-chloroisoquinoline (1eq, 7.80mmol, 1.27g) in CH₂Cl₂ (30mL) was stirred for 2 hours at room temperature. The reaction mixture was diluted with CH₂Cl₂ (20mL) and MeOH (10mL) and the organic phase was washed with 2M NaOH solution. The aqueous layer
10 was extracted with CH₂Cl₂. The organic fractions were combined, dried over MgSO₄, filtered and evaporated to yield the title compound (6.20mmol, 1.12g, 79%) as an orange solid.

Step 2 : 5-Chloroisoquinolin-1(2H)-one

15 According to Scheme 28 Step 2: A solution of 5-chloroisoquinoline N-oxide (1eq, 6.88mmol, 1.25g) in anhydride acetic (20mL) was stirred for 3 hours under reflux and overnight at room temperature. After distillation of anhydride acetic, a solution of NaOH (2M, 10mL) was added and the reaction mixture was stirred for 1 hour at 50-60°C. Then the reaction mixture was acidified (pH=6) with citric acid (5% in water).
20 The precipitate was filtered, washed with water, dried under vacuum. The crude residue was taken up in CH₂Cl₂ (20mL). The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated to yield the title compound (3.73mmol, 0.67g, 100%) as a brown solid.

25 *Step 3 : 5-Chloro-2-propylisoquinolin-1(2H)-one*

According to Scheme 28 Step 3: The title compound was prepared from 5-chloroisoquinolin-1(2H)-one (1eq, 2.66mmol, 0.48g) and 1-bromopropyl (1.1eq,

2.93mmol, 0.27mL) according to the procedure described for Example 1 Step 2. Reaction conditions: microwaved at 150°C for 60 min. in acetone. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart preppacked column 25g SiO₂) using pure CH₂Cl₂ to afford 5-chloro-2-propylisoquinolin-1(2H)-one
5 (1.06mmol, 0.24g, 40%) as an orange solid.

Step 4 : 5-(4-Methoxyphenethylamino)-2-propylisoquinolin-1(2H)-one

According to Scheme 28 Step 4: To a mixture of 5-chloro-2-propylisoquinolin-1(2H)-one (1eq, 1.08mmol, 0.24g), NaOtBu (1.5eq, 1.62mmol, 0.16g), Pd₂(dba)₃ (0.05eq, 54μmol, 50mg), BINAP (0.05eq, 54μmol, 34mg) in degassed and dried toluene (4mL)
10 was added (1.5eq, 1.62mmol, 0.25g). The reaction mixture was microwaved at 180°C for 2 hours and 1 hour at 200°C. The reaction mixture was quenched with water and the aqueous phase was extracted with CH₂Cl₂. The organic fraction was washed with saturated NH₄OH solution, brine, dried over Na₂SO₄, filtered and concentrated under
15 reduced pressure. The crude product was purified by silica gel chromatography (AIT Flashsmart preppacked column SiO₂, cyclohexane/AcOEt 90/10) to afford 5-(4-methoxyphenethylamino)-2-propylisoquinolin-1(2H)-one (0.39mmol, 0.13g, 36%) as a white solid.

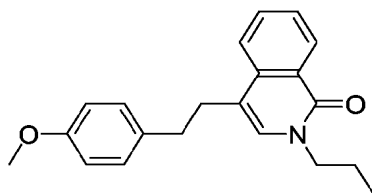
R_f = 0.05 (cyclohexane/AcOEt 80/20); M.p.: 109-110°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.60min; MS *m/z* (CI) [MH]⁺ = 337.
20

Step 5 : 5-(4-Hydroxyphenethylamino)-2-propylisoquinolin-1(2H)-one

The title compound was prepared from 5-(4-methoxyphenethylamino)-2-propylisoquinolin-1(2H)-one (1eq, 0.20mmol, 66mg) according to the procedure
25 described for Example 20 Step 2. The crude product was purified by trituration in diisopropyl ether to yield after filtration 5-(4-hydroxyphenethylamino)-2-propylisoquinolin-1(2H)-one (64μmol, 20mg, 32%) as a brown powder

M.p.: 170-171°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.78min; MS *m/z* (CI) [MH]⁺ = 323; ¹H NMR (300 MHz, DMSO-d⁶) δ 0.96 (t, J=7.4Hz, 3H), 1.40-
30 1.72 (br. s, 1H), 1.72-1.87 (m, 2H), 2.99 (t, J=7.2Hz, 2H), 3.47 (t, J=6.9Hz, 2H), 3.95 (t, J=7.4Hz, 2H), 6.35-6.47 (m, 1H), 6.79 (d, J=8.4Hz, 2H), 6.99-7.12 (m, 4H), 7.34-7.42 (m, 1H), 7.91-8.02 (m, 1H).

EXAMPLE 39 : 4-(4-Methoxyphenethyl)-2-propylisoquinolin-1(2H)-one (Final Compound 14-01)



5 *Step 1 : 4-(2-(4-Methoxyphenyl)ethynyl)isoquinoline*

According to Scheme 29 Step 1: The title compound was prepared from 4-bromoisoquinoline (1eq, 5.30mmol, 1.10g) and 1-ethynyl-4-methoxybenzene (1eq, 5.30mmol, 0.70g) according to the procedure described for Example 13 Step 1. Reaction conditions: 70°C for 4 hours. The crude product was purified by silica gel
10 chromatography (AIT Flashsmart preppacked column SiO₂, cyclohexane/AcOEt 90/10 to 80/20) to afford 4-(2-(4-methoxyphenyl)ethynyl)isoquinoline (3.11mmol, 0.81g, 59%) as a white solid.

LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 5.19min; MS *m/z* (CI) [MH]⁺= 260.

15

Step 2 : 4-(4-Methoxyphenethyl)isoquinoline

According to Scheme 29 Step 2: The title compound was prepared from 4-(2-(4-methoxyphenyl)ethynyl)isoquinoline (1eq, 3.11mmol, 0.81g) according to the procedure described for Example 13 Step 2. Reaction conditions: overnight at 50°C.
20 The crude product was purified by silica gel chromatography (AIT Flashsmart preppacked column SiO₂ 30g, cyclohexane/AcOEt 85/15) to afford 4-(4-methoxyphenethyl)isoquinoline (1.33mmol, 0.35g, 43%) as a yellow oil.

LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.26min; MS *m/z* (CI) [MH]⁺= 264.

25

Step 3 : 4-(4-Methoxyphenethyl)isoquinoline-N-oxide

According to Scheme 29 Step 3: The title compound was prepared from 4-(4-methoxyphenethyl)isoquinoline (1eq, 1.33mmol, 0.35g) according to the procedure described for Example 38 Step 1. The crude product was used without being purified

and yielded 4-(4-methoxyphenethyl)isoquinoline-N-oxide (1.33mmol, 0.37g, 100%) as an orange solid.

Step 4 : 4-(4-Methoxyphenethyl)isoquinolin-1(2H)-one

- 5 According to Scheme 29 Step 4: The title compound was prepared from 4-(4-methoxyphenethyl)isoquinoline-N-oxide (1eq, 1.33mmol, 0.37g) according to the procedure described for Example 38 Step 2. The crude product was used without being purified and yielded 4-(4-methoxyphenethyl)isoquinolin-1(2H)-one (0.36mmol, 0.10g, 27%) as a brown solid.

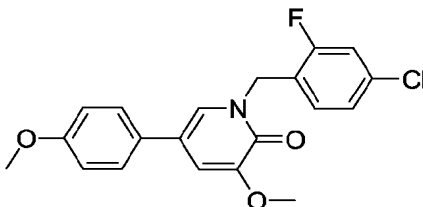
10

Step 5 : 4-(4-Methoxyphenethyl)-2-propylisoquinolin-1(2H)-one

- According to Scheme 29 Step 5: The title compound was prepared from 4-(4-methoxyphenethyl)isoquinolin-1(2H)-one (1eq, 0.36mmol, 0.10g) 1-bromopropane (1.5eq, 0.54mmol, 49 μ L) according to the procedure described for Example 1 Step 2.
- 15 Reaction conditions: microwaved at 180°C for 15min. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepac column 25g SiO₂) using CH₂Cl₂/MeOH 99.5/0.5 to afford 4-(4-methoxyphenethyl)-2-propylisoquinolin-1(2H)-one (47 μ mol, 15mg, 13%) as an orange oil.

- LC (XTerra RP₁₈, 3.5 μ m, 3.0x50mm Column): RT = 4.89min; MS *m/z* (CI) [MH]⁺= 322; ¹H NMR (300 MHz, CDCl₃) δ 0.83 (t, J=7.4Hz, 3H), 1.55-1.70 (m, 2H), 2.75-2.90 (4H), 3.72 (s, 3H), 3.81 (t, J=7.3Hz, 2H), 6.60 (s, 1H), 6.75 (d, J=8.7Hz, 2H), 6.97 (d, J=8.6Hz, 2H), 7.40-7.50 (m, 1H), 7.62-7.68 (m, 2H), 8.40-8.45 (m, 1H).
- 20

- EXAMPLE 40 : 1-(4-Chloro-2-fluorobenzyl)-3-methoxy-5-(4-methoxyphenyl)pyridin-2(1H)-one (Final Compound 9-10)**
- 25



Step 1 : 5-Bromo-2,3-dimethoxypyridine

The title compound was prepared from 2,3-dimethoxypyridine (1eq, 7.19mmol, 1.00g) according to the procedure described for Example 1 Step 1. Reaction conditions: 48 hours at room temperature. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g SiO₂) using cyclohexane/AcOEt 96/4 to afford 5-bromo-2,3-dimethoxypyridine (3.81mmol, 0.83g, 53%).

Step 2 : 2,3-Dimethoxy-5-(4-methoxyphenyl)pyridine

According to Scheme 4 Method B: The title compound was prepared from 5-bromo-2,3-dimethoxypyridine (1eq, 1.83mmol, 0.40g) and 4-methoxyphenyl boronic acid (1eq, 1.83mmol, 0.28g) according to the procedure described for Example 1 Step 3. The crude product was purified by flash chromatography on silica gel using cyclohexane/AcOEt 90/10 as eluent to afford the title compound 2,3-dimethoxy-5-(4-methoxyphenyl)pyridine (0.82mmol, 0.20g, 45%) was obtained.

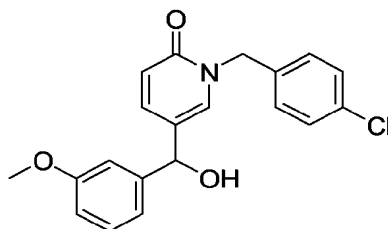
LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.27 min; MS *m/z* (CI) [MH]⁺ = 246.

Step 3 : 1-(4-Chloro-2-fluorobenzyl)-3-methoxy-5-(4-methoxyphenyl)pyridin-2(1H)-one

According to Scheme 4 Step 1: The title compound was prepared from 2,3-dimethoxy-5-(4-methoxyphenyl)pyridine (1eq, 0.41mol, 0.10g) and 1-(bromomethyl)-4-chloro-2-fluorobenzene (2eq, 0.82mmol, 0.18g) according to the procedure described for Example 6 Step 2. Reaction conditions: 14 hours at 80°C in acetonitrile. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 10g SiO₂) using cyclohexane/AcOEt 70/30 to 50/50 as eluent to afford 1-(4-Chloro-2-fluorobenzyl)-3-methoxy-5-(4-methoxyphenyl)pyridin-2(1H)-one (0.24mmol, 0.09g, 59%).

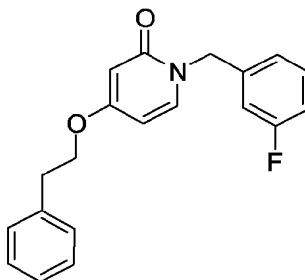
LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.53min; MS *m/z* (CI) [MH]⁺ = 374, 376; ¹H NMR (300MHz, CDCl₃) δ 3.83 (s, 3H), 3.87 (s, 3H), 5.22 (s, 2H), 6.82 (d, J=2.3Hz, 1H), 6.95 (d, J=8.7Hz, 2H), 7.07-7.12 (m, 2H), 7.13-7.15 (m, 1H), 7.32 (d, J=9.0Hz, 2H), 7.47-7.55 (m, 1H).

EXAMPLE 41 : 1-(4-Chlorobenzyl)-5-(hydroxy(3-methoxyphenyl)methyl)pyridin-2(1H)-one (Final Compound 3-10)



- 5 According to Scheme 7 Method B: A solution of 3-methoxybenzylmagnesium bromide (1.2eq, 1.00mmol, 1.00mL) was added dropwise to a solution of 1-(4-chlorobenzyl)-1,6-dihydro-6-oxopyridine-3-carbaldehyde (1eq, 1.21mmol, 0.30g, Example 10 Step 1) in THF (15mL) at -78°C under a nitrogen atmosphere. The reaction mixture was stirred for 14 hours at room temperature. The resulting mixture was poured onto ice and
- 10 extracted with CH₂Cl₂. The organic layer was dried over MgSO₄, filtered and evaporated. Purification by flash chromatography (AIT Flashsmart prepac column 25g SiO₂, CH₂Cl₂/AcOEt 80/20 to 70/30) afford 1-(4-chlorobenzyl)-5-(hydroxy(3-methoxyphenyl)methyl)pyridin-2(1H)-one (0.64mmol, 0.28g, 64%) as a yellow semi-solid.
- 15 LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.76 min; MS *m/z* ES⁺ = 356, 358; ¹H NMR (500MHz, CDCl₃) δ 2.13 (d, J=3.4Hz, 1H), 3.80 (s, 3H), 5.09 (s, 2H), 5.56 (d, J=3.5Hz, 1H), 6.57 (d, J=9.4Hz, 1H), 6.84-6.90 (3H), 7.22-7.35 (5H).

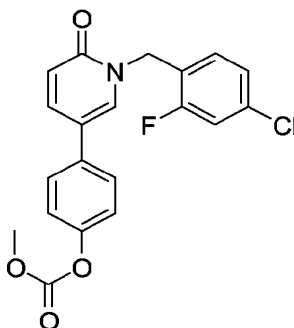
EXAMPLE 42 : 1-(3-Fluorobenzyl)-4-phenethoxy pyridin-2(1H)-one (Final Compound 7-03)



According to Scheme 13 Method A: The title compound was prepared from 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1*H*)-one (1eq, 0.23mmol, 0.05g, Example 19 Step 2) and 1-(2-bromoethyl)benzene (2eq, 0.46mmol, 0.06mL) according to the procedure described for Example 1 Step 2. Microwave conditions: 180°C for 900s in acetonitrile (2mL). The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g SiO₂) using CH₂Cl₂/AcOEt 80/20 and by recrystallization in pentane to afford 1-(3-fluorobenzyl)-4-phenethoxypyridin-2(1*H*)-one (0.13mmol, 43mg, 58%) as a white solid.

M.p.: 93°C; LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.41min; MS *m/z* (CI) [MH]⁺ = 324; ¹H NMR (500MHz, DMSO-*d*⁶) δ 3.00 (t, J=6.7Hz, 2H), 4.18 (t, J=6.7Hz, 2H), 5.01 (s, 2H), 5.84 (d, J=2.7Hz, 1H), 5.95 (dd, J=2.7Hz and 7.6Hz, 1H), 7.03-7.11 (3H), 7.18-7.25 (m, 1H), 7.29 (d, J=4.7Hz, 4H), 7.32-7.38 (m, 1H), 7.66 (d, J=7.6Hz, 1H).

EXAMPLE 43 : 4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl) phenyl methyl carbonate (Final Compound 6-39)



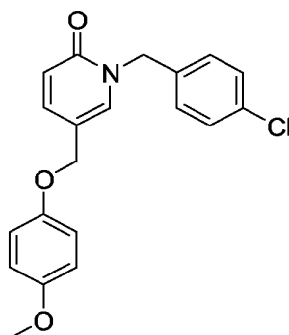
According to Scheme 14 Method B: A suspension of 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1*H*)-one (1eq, 0.61mmol, 0.20g, Example 20 Step 2), K₂CO₃ (10eq, 6.10mmol, 0.84g) and methylchloroformate (4eq, 2.43mmol, 0.19mL) in THF (10mL) was stirred overnight at room temperature. Water was added to the reaction mixture, then the aqueous phase was extracted with AcOEt. The organic phase was dried over MgSO₄, filtered and evaporated. The resulting crude oil was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 10g SiO₂) using CH₂Cl₂/AcOEt 90/10 then was washed with Et₂O and was dried to afford 4-(1-(4-

chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl methyl carbonate (0.36mmol, 139mg, 59%) as a white solid.

M.p.: 124°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.28min; MS *m/z* (CI) [MH]⁺ = 388, 390; ¹H NMR (300MHz, CDCl₃) δ 3.84 (s, 3H), 5.19 (s, 2H), 6.53 (d, J=9.6Hz, 1H), 7.17-7.27 (m, 2H), 7.27-7.33 (3H), 7.45 (dd, J=2.1Hz and 9.9Hz, 1H), 7.58-7.66 (m, 2H), 7.88 (dd, J=2.7Hz and 9.9Hz, 1H), 8.23 (d, J=2.7Hz, 1H).

EXAMPLE 44 : 1-(4-Chlorobenzyl)-5-((4-methoxyphenoxy)methyl)pyridin-2(1H)-one (Final Compound 16-02)

10



Step 1 : 1-(4-Chlorobenzyl)-5-(hydroxymethyl)pyridin-2(1H)-one

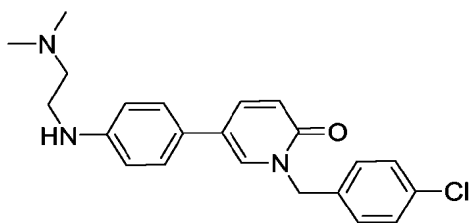
According to Scheme 16 Method B: A solution of 1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carbaldehyde (1eq, 1.41mmol, 0.35g, Example 10 Step 1) and DIBAL (3eq, 4.20mmol, 4.20mL) in THF (5mL) was stirred for 30 min. at -78°C and 1 hour at room temperature. After addition of AcOEt, the reaction mixture was diluted with water. The organic layer was washed with saturated NH₄Cl solution, dried over Na₂SO₄, filtered through celite and evaporated. The resulting crude residue was purified by silica gel chromatography (AIT Flashsmart prepac column 25g SiO₂) using CH₂Cl₂/MeOH 95/5 to afford 1-(4-chlorobenzyl)-5-(hydroxymethyl)pyridin-2(1H)-one (0.45mmol, 0.11g, 32%) as an orange oil.

LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 2.86min; MS *m/z* (CI) [MH]⁺ = 250, 252.

Step 2 : 1-(4-Chlorobenzyl)-5-((4-methoxyphenoxy)methyl)pyridin-2(1H)-one

According to Scheme 16 Method B: 4-Methoxyphenol (1.5eq, 0.68mmol, 84.3mg), PPh₃ (2.0eq, 0.91mmol, 0.30g) and DEAD (2eq, 0.91mmol, 0.16g) were added to a solution of 1-(4-chlorobenzyl)-5-(hydroxymethyl)pyridin-2(1H)-one (1eq, 0.45mmol, 0.11g) in THF (5mL). The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the reaction mixture was diluted with water. The organic layer was washed with saturated NaHCO₃ solution, dried over Na₂SO₄, filtered and evaporated. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO₂) using cyclohexane/AcOEt 80/20 to afford 1-(4-chlorobenzyl)-5-((4-methoxyphenoxy)methyl)pyridin-2(1H)-one (0.19mmol, 0.07g, 42%) as a white solid.

M.p.: 114°C. LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 4.36min; MS *m/z* (CI) [MH]⁺ = 356, 358. ¹H NMR (500MHz, DMSO-d₆) δ 3.69 (s, 3H), 4.74 (s, 2H), 5.07 (s, 2H), 6.45 (d, J=9.3Hz, 1H), 6.82-6.87 (m, 2H), 6.88-6.93 (m, 2H), 7.29 (d, J=8.5Hz, 2H), 7.40 (d, J=8.5Hz, 2H), 7.52 (dd, J=2.5Hz and 9.0Hz, 1H), 7.93 (d, J=2.3Hz, 1H).

EXAMPLE 45 : 1-(4-Chlorobenzyl)-5-(4-(2-(dimethylamino)ethylamino)phenyl)pyridin-2(1H)-one (Final Compound 2-50)*Step 1 : tert-Butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl carbamate*

According to Scheme 19 Step 1: A suspension of 1-(4-chlorobenzyl)-5-bromopyridin-2(1H)-one (3.35mmol, 1.00g, Example 2 Step 1), N-tert-butoxycarbonyl-4-aminophenylboronic acid (6.03mmol, 1.42g), Pd(PPh₃)₄ (0.17mmol, 195mg), Na₂CO₃ (13.4mmol, 1.42g) in DME (20mL) and H₂O (5mL) was degassed to remove the oxygen. The mixture was heated at 85°C for 20 hours. The resulting suspension was filtered off and the filtrate was washed with CH₂Cl₂. The organic solvent was

separated, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3)\text{sat. } 98/2$. The product fractions were collected and the solvent was evaporated to yield the title compound (627mg, 46%).

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Step 2 : tert-Butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl(2-(dimethylamino)ethyl)carbamate

According to Scheme 19 Step 4: *tert*-Butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenylcarbamate (0.34mmol 0.14g) was dissolved in dry THF (4mL) and the resulting solution was cooled at 0°C . Then, NaH (60% mineral oil; 1.02mmol, 40.8mg) was added, the mixture was stirred at 0°C for 10 minutes, warmed at room temperature and stirred for 30 minutes. After, N,N-dimethylaminoethyl chloride (0.69mmol) and KI (0.34mmol, 57.0mg) were added and the reaction mixture was heated at 90°C for 16 hours. The resulting suspension was taken up in CH_2Cl_2 , washed with water, washed with brine, filtered off and the filtrate was washed with CH_2Cl_2 . The organic solvent was separated, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge ($\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3)\text{sat. } 95/5$). The product fractions were collected and the solvent was evaporated to yield *tert*-butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl(2-(dimethylamino)ethyl)carbamate (87.9mg)

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Step 3 : 1-(4-Chlorobenzyl)-5-(4-(2-(dimethylamino)ethylamino)phenyl)pyridin-2(1H)-one

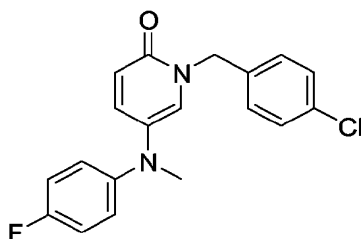
According to Scheme 19 Step 5: *tert*-Butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl(2-(dimethylamino)ethyl)carbamate (0.16mmol, 79.0mg) was dissolved in dry CH_2Cl_2 (30mL). Then TFA (7mL) was added dropwise and the resulting solution was stirred at room temperature for 3 hours. Then the solvent was evaporated under reduced pressure and the resulting residue thus obtained was resulting suspension was taken up in CH_2Cl_2 , washed with a saturated aqueous NaHCO_3 solution. The organic solvent was separated, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3)\text{sat. } 95/5$. The product fractions were

30

collected and the solvent was evaporated to yield 1-(4-chlorobenzyl)-5-(4-(2-(dimethylamino)ethylamino)phenyl)pyridin-2(1H)-one (16.4mg, 26%)

LC (ACE Column): RT = 3.23min; MS m/z (CI) $[MH]^+ = 382$; 1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, 1H, $J=9.5$, 2.6 Hz); 7.34 (d, 1H, $J=2.6$ Hz); 7.26-7.33 (m, 4H); 7.17 (d, 2H, $J=8.7$ Hz); 6.67 (d, 1H, $J=9.5$ Hz); 6.64 (d, 2H, $J=8.4$ Hz); 5.15 (s, 2H); 4.43 (s, 1H); 3.16 (t, 2H, $J=5.8$ Hz); 2.58 (t, 2H, $J=5.8$ Hz); 2.27 (s, 6H).

EXAMPLE 46 : 1-(4-Chlorobenzyl)-5-((4-fluorophenyl)(methyl)amino)pyridin-2(1H)-one (Final Compound 3-21)



Step 1 : N-(4-Fluorophenyl)-6-methoxy-N-methylpyridin-3-amine

According to Scheme 22 Method B: To a mixture of 5-bromo-2-methoxypyridine (1eq, 1.06mmol, 0.14mL), K_{Ot}Bu (1.5eq, 1.60mmol, 0.18g), Pd(OAc)₂ (0.02eq, 21 μ mol, 48mg), BINAP (0.04eq, 42 μ mol, 26mg) in degassed DMF (1.5mL) was added 4-fluoro-N-methylbenzenamine (1.2eq, 1.28mmol, 0.14mL). The reaction mixture was microwaved at 130°C for 5min. The reaction mixture was quenched with water and the aqueous phase was extracted with AcOEt. The organic fraction was washed brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (AIT Flashsmart prepac column 15g SiO₂, CH₂Cl₂/AcOEt 90/10) to afford N-(4-fluorophenyl)-6-methoxy-N-methylpyridin-3-amine (0.08mmol, 20mg, 8%) as a yellow oil.

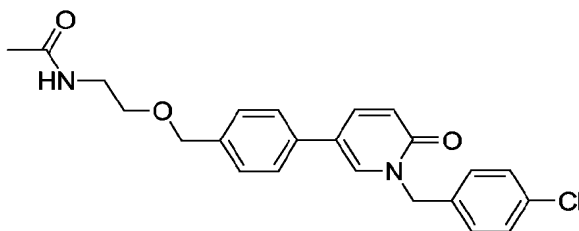
R_f = 0.45 (CH₂Cl₂/AcOEt 80/20); LC (XTerra RP₁₈, 3.5 μ m, 3.0x50mm Column): RT = 2.49min; MS m/z (CI) $[MH]^+ = 233$.

Step 2 : 1-(4-Chlorobenzyl)-5-((4-fluorophenyl)(methyl)amino)pyridin-2(1H)-one

According to Scheme 22 Step 2: The title compound was prepared from N-(4-fluorophenyl)-6-methoxy-N-methylpyridin-3-amine (1eq, 86 μ mol, 20mg) and 4-

chloro-benzylbromide (1.7eq, 0.15mmol, 30mg) according to the procedure described for Example 6 Step 2. Reaction conditions: 12 hours at 80°C in acetonitrile. The crude product was purified by silica gel chromatography (AIT Flashsmart prepac column 10g SiO₂) using CH₂Cl₂/AcOEt 50/50 as eluent to afford 1-(4-chlorobenzyl)-5-((4-fluorophenyl)(methyl)amino)pyridin-2(1H)-one (29μmol, 10mg, 34%) as a yellow oil. R_f = 0.20 (CH₂Cl₂/AcOEt 90/10); LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.36min; MS *m/z* (CI) [MH]⁺ = 343, 345; ¹H NMR (300MHz, CDCl₃) δ 3.24 (s, 3H), 5.02 (s, 2H), 5.56 (dd, J=2.7Hz and 7.7Hz, 1H), 5.74 (d, J=2.7Hz, 1H), 6.92 (d, J=7.7Hz, 1H), 7.07-7.12 (m, 2H), 7.13-7.18 (m, 2H), 7.23 (d, J=8.4Hz, 2H), 7.30 (d, J=8.4Hz, 2H).

EXAMPLE 47 : N-(2-(4-(1-(4-Chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)benzyloxy)ethyl)acetamide (Final Compound 2-42)



Step 1 : 1-(4-Chlorobenzyl)-5-(4-(bromomethyl)phenyl)pyridin-2(1H)-one

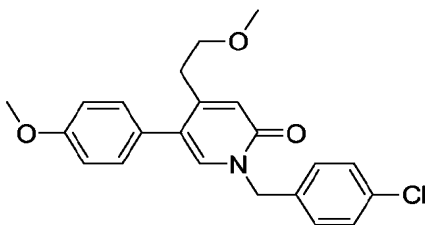
According to Scheme 25 Step 3: To a solution of 1-(4-chlorobenzyl)-5-(4-(hydroxymethyl)phenyl)pyridin-2(1H)-one (1eq, 3.07mmol, 1.00g, Example 35 Step 1) in THF (8mL) were added NBS (1.22eq, 3.74mmol, 0.67g) and PPh₃ (1.20eq, 3.68mmol, 0.97g) at -20°C for 4 hours. After evaporation of the solvent, the crude product was purified by silica gel chromatography (AIT Flashsmart prepac column 50g SiO₂) using CH₂Cl₂/MeOH 98/2 to afford 1-(4-chlorobenzyl)-5-(4-(bromomethyl)phenyl)pyridin-2(1H)-one (2.06mmol, 0.80g, 67%). LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.71min; MS *m/z* (CI) [MH]⁺ = 388, 390.

Step 2 : N-(2-(4-(1-(4-Chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)benzyloxy)ethyl)acetamide

According to Scheme 25 Step 4: The title compound was prepared from 1-(4-chlorobenzyl)-5-(4-(bromomethyl)phenyl)pyridin-2(1*H*)-one (1eq, 0.26mmol, 0.10g) and (1.5eq, 0.39mmol, 0.04g) according to the procedure described for Example 34 Step 3. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 5g SiO₂) using CH₂Cl₂/MeOH 98/2 as the eluent to afford *N*-(2-(4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)benzyloxy)ethyl)acetamide (0.13mmol, 54mg, 51%) as a white solid.

M.p.: 152°C; LC (XTerra RP₁₈, 3.5µm, 3.0x50mm Column): RT = 3.55min; MS *m/z* (CI) [MH]⁺ = 411, 413; ¹H NMR (300MHz, DMSO-d₆) δ 1.80 (s, 3H), 3.18-3.27 (m, 2H), 3.42 (t, J=6.0Hz, 2H), 4.48 (s, 2H), 5.16 (s, 2H), 6.52 (d, J=9.6Hz, 1H), 7.35-7.42 (6H), 7.56 (d, J=7.8Hz, 2H), 7.86 (dd, J=2.7Hz and 9.6Hz, 2H), 8.28 (d, J= 2.7Hz, 1H).

Example 48 : 1-(4-Chlorobenzyl)-4-(2-methoxyethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 9-17)



Step 1 : 2-Methoxy-5-(4-methoxyphenyl)-4-methylpyridine

According to Scheme 30 Step 1: The title compound was prepared from 5-bromo-2-methoxy-4-methylpyridine (1eq, 15.8mmol, 3.20g) and 4-methoxyphenylboronic acid (1.5eq, 23.8mmol, 3.61g) according to the procedure described for Example 1 Step 3. Reaction conditions: 21 hours at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 130g SiO₂) using AcOEt/MeOH (95/5) as the eluent to afford 2-methoxy-5-(4-methoxyphenyl)-4-methylpyridine (12.8mmol, 2.94g, 81%) as a light yellow solid.

LC (Zorbax C₁₈, 3.5µm, 4.60x50mm Column): RT = 4.52min; MS *m/z* (CI) [MH]⁺ = 230.

Step 2 : 2-(2-Methoxy-5-(4-methoxyphenyl)pyridin-4-yl)ethanol

According to Scheme 30 Step 2: To a stirred solution of 2-methoxy-5-(4-methoxyphenyl)-4-methylpyridine (1eq, 10.0mmol, 2.30g) in anhydrous THF (66mL) at -78°C under argon was added dropwise butyl lithium (2.5M, 1.5eq, 15.1mmol, 6.0mL). The reaction mixture was stirred for one hour and then allowed to warm slowly to 0°C and stirred at 0°C for a further 30 minutes. The reaction mixture was then cooled to -78°C and paraformaldehyde (6.07g) was added. The reaction mixture was then allowed to warm to room temperature and was stirred for 2 hours. The reaction was quenched with saturated aqueous NH₄Cl (30mL), diluted with AcOEt and the aqueous phase was extracted (x3). The combined organic fractions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. HCl 3M (15mL) was added to the solution of the crude residue diluted in acetonitrile (10mL). The reaction mixture was stirred for 2 hours at 60°C. The aqueous phase was extracted with Et₂O, then neutralized with NaHCO₃ (40mL). The aqueous phase was extracted with CH₂Cl₂. The combined organic fractions were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 20g SiO₂) using CH₂Cl₂/AcOEt (99/1) as the eluent to afford 2-(2-methoxy-5-(4-methoxyphenyl)pyridin-4-yl)ethanol (0.62mmol, 0.16g, 6%) as a colorless oil.

LC (Zorbax C₁₈, 3.5µm, 4.6x50mm Column): RT = 3.42min; MS *m/z* (CI) [MH]⁺ = 260.

Step 3 : 1-(4-Chlorobenzyl)-4-(2-hydroxyethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

According to Scheme 30 Step 3: The title compound was prepared from 2-(2-methoxy-5-(4-methoxyphenyl)pyridin-4-yl)ethanol (1eq, 0.62mmol, 0.16g) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 0.93mmol, 0.19g) according to the procedure described for Example 6 Step 2. Reaction conditions: 19 hours under 90°C. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 10g SiO₂) using CH₂Cl₂/MeOH 98/2 as eluent afford 1-(4-chlorobenzyl)-4-(2-hydroxyethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (0.22mmol, 82mg, 36%) as a pale yellow solid.

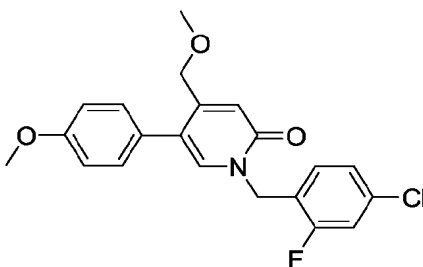
LC (Zorbax C₁₈, 3.5µm, 4.6x50mm Column): RT = 3.83min; MS *m/z* (CI) [MH]⁺= 370, 372.

Step 4 : 1-(4-Chlorobenzyl)-4-(2-methoxyethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

5 According to Scheme 30 Step 4: The title compound was prepared from 1-(4-chlorobenzyl)-4-(2-hydroxyethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (1eq, 0.14mmol, 50mg) and iodomethane (3eq, 0.41mmol, 58mg) according to the procedure described for Example 34 Step 3. The product was further purified by flash chromatography over silica gel (AIT Flashsmart prepac column 5g SiO₂) using
10 Et₂O/pentane 90/10 to afford 1-(4-chlorobenzyl)-4-(2-methoxyethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (0.12mmol, 47mg, 91%) as a colorless oil.

LC (Zorbax C₁₈, 3.5µm, 4.6x50mm Column): RT = 4.49min; MS *m/z* (CI) [MH]⁺= 384, 386; ¹H NMR (300MHz, CDCl₃) δ 2.65 (t, J=6.7Hz, 2H), 3.25 (s, 3H), 3.44 (t, J=6.7Hz, 2H), 3.82 (s, 3H), 5.09 (s, 2H), 6.58 (s, 1H), 6.90 (d, J=8.7Hz, 2H), 7.06 (s,
15 1H), 7.11 (d, J=8.7Hz, 2H), 7.23-7.32 (4H).

EXAMPLE 49 : 1-(4-Chloro-2-fluorobenzyl)-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (Final Compound 9-16)



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Step 1 : 4-(Bromomethyl)-2-methoxy-5-(4-methoxyphenyl)pyridine

According to Scheme 31 Step 2: To a solution of 2-methoxy-5-(4-methoxyphenyl)-4-methylpyridine (2.20mmol, 0.50g, Example 48 Step 1) in CCl₄ (10mL) was added NBS (2eq, 4.40mmol, 0.78g). The reaction was then heated to reflux and subjected to UV
25 light for 48 hours. The reaction was allowed to cool, filtered and concentrated under reduced pressure to afford crude 4-(bromomethyl)-2-methoxy-5-(4-methoxyphenyl)pyridine (0.70g) as a yellow oil which was used without any purification in the next step.

LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.87min; MS *m/z* (CI) [MH]⁺= 307, 309.

Step 2 : 2-Methoxy-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridine

5 According to Scheme 31 Step 3: The title compound was prepared from 4-(bromomethyl)-2-methoxy-5-(4-methoxyphenyl)pyridine (1eq, 2.30mmol, 0.70g) according to the procedure described for Example 33 Step 1. After work up, 2-methoxy-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridine (0.66mmol, 0.17g) as a light yellow oil.

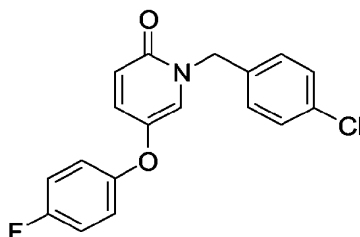
10 LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.56min; MS *m/z* (CI) [MH]⁺= 260.

Step 3 : 1-(4-Chloro-2-fluorobenzyl)-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

15 According to Scheme 31 Step 4: The title compound was prepared from 2-methoxy-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridine (1eq, 0.66mmol, 0.17g) and 1-(bromomethyl)-4-chloro-2-fluorobenzene (1.5eq, 0.98mmol, 0.22g) according to the procedure described for Example 6 Step 2. Reaction conditions: 12 hours at 80°C. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked
20 column 25g SiO₂) using CH₂Cl₂/MeOH 98/2 as the eluent to afford 1-(4-chloro-2-fluorobenzyl)-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (5μmol, 2mg, 1%) as yellow oil.

LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 3.83min; MS *m/z* (CI) [MH]⁺= 388, 390; ¹H NMR (300MHz, CDCl₃) δ 1.64 (s, 2H), 2.07 (s, 3H), 3.83 (s, 3H), 5.12 (s,
25 2H), 6.48 (s, 1H), 6.93 (d, J=9.0Hz, 2H), 7.13-7.28 (m, 5H), 7.40-7.46 (m, 1H).

EXAMPLE 50 : 1-(4-Chlorobenzyl)-5-(4-fluorophenoxy)pyridin-2(1H)-one (Final Compound 3-13)



5 *Step 1 : 5-(4-Fluorophenoxy)-2-methoxypyridine*

According to Scheme 32 Method A: 5-Bromo-2-methoxypyridine (5.32mmol, 1.00g), 4-fluorobenzylalcohol (7.98mmol, 0.90g), N,N-dimethylaminoacetic acid (15.9mmol, 1.69g), CuI (5.32mmol, 1.01g), CsCO₃ (12.4mmol, 4.05g) in dioxane (25mL) and DMF (2.5mL) were heated at 150°C for 25 min. under microwave irradiation
10 conditions. Then the cooled crude reaction was filtered off over celite. The filtrate was washed with saturated aqueous NH₄Cl solution and extracted with AcOEt. The organic layer was separated, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge (heptane/AcOEt, 80/20). The product fractions were collected and the solvent was
15 evaporated to give a mixture of the desired product contaminated with 4-fluorobenzylalcohol. This residue was taken up in AcOEt and washed with aqueous solution of NaOH 1N. The organic layer was separated, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure giving 5-(4-fluorophenoxy)-2-methoxypyridine (520mg, 45%).

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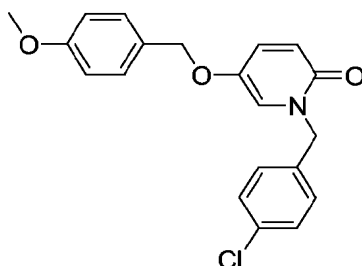
Step 2 : 1-(4-Chlorobenzyl)-5-(4-fluorophenoxy)pyridin-2(1H)-one

According to Scheme 32 Step 1: 5-(4-Fluorophenoxy)-2-methoxypyridine (2.37mmol, 520mg), 4-chlorobenzylchloride (3.55mmol, 603mg), NaI (2.37mmol, 356mg) in acetonitrile (15mL) was heated at 150°C for 20 minutes under microwave conditions.
25 The cooled crude reaction was washed with water, extracted with AcOEt. The organic layer was collected, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge (heptane/AcOEt, 90:10 to CH₂Cl₂) and then CH₂Cl₂/acetone 90:10), following HPLC

purification yielding 1-(4-chlorobenzyl)-5-(4-fluorophenoxy)pyridin-2(1*H*)-one
(211mg, 27%).

LC (ACE Column): RT = 4.56min; MS *m/z* (CI) [MH]⁺ = 330.

**5 EXAMPLE 51 : 1-(4-Chlorobenzyl)-5-(4-methoxybenzyloxy)pyridin-2(1*H*)-one
(Final Compound 3-17)**



Step 1 : 2-Methoxy-5-(4-methoxybenzyloxy)pyridine

- 10 According to Scheme 32 Method B: To a mixture of 2-methoxy-5-hydroxypyridine (2.87mmol, 0.36g), 4-methoxybenzyl alcohol (5.75mmol, 0.72mL) and PPh₃ (5.29mmol, 1.4g) in THF (3.75mL) cooled with an ice-water bath, was added dropwise DEAD (5.47mmol, 0.86ml). The resulting mixture was irradiated under microwave conditions at 90°C for 30 minutes. The resulting reaction mixture was cooled, washed
- 15 with a 1 N NaOH solution and extracted with AcOEt. The organic layer was separated, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue triturated with diisopropyl ether. The precipitated obtained (PPh₃O) was filtered off. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge heptane/CH₂Cl₂ 80/20 yielding 2-methoxy-5-(4-methoxybenzyloxy)pyridine (339mg,
- 20 48%).

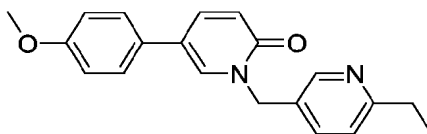
*Step 2 : 1-(4-Chlorobenzyl)-5-(4-methoxybenzyloxy)pyridine-2(1*H*)-one*

- According to Scheme 32 Step 1: 2-Methoxy-5-(4-methoxybenzyloxy)pyridine (1.38mmol, 339mg), 4-chlorobenzylchloride (2.76mmol, 468mg), NaI (1.38mmol, 207mg) in acetonitrile (15mL) was heated at 150°C for 50 minutes under microwave
- 25 conditions. The cooled crude reaction was washed with water, extracted with AcOEt. The organic layer was collected, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica

cartridge CH₂Cl₂ and CH₂Cl₂/acetone 90/10) yielding 1-(4-chlorobenzyl)-5-(4-methoxybenzyloxy)pyridine-2(1*H*)-one (141mg, 29%).

LC (ACE Column): RT = 4.39min; MS *m/z* (CI) [MH]⁺ = 355; ¹H NMR (400 MHz, CDCl₃) δ 7.27-7.32 (m, 2H); 7.19-7.25 (m, 3H); 7.14-7.19 (m, 2H, *J*=8.3 Hz); 6.85-6.90 (m, 2H); 6.72 (d, 1H, *J*=3.1 Hz); 6.58 (d, 1H, *J*=9.7 Hz); 5.03 (s, 2H); 4.75 (s, 2H); 3.82 (s, 3H)

EXAMPLE 52 : 1-((6-Ethylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 4-45)



*Step 1 : 1-((6-Chloropyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one*

5-(4-Methoxyphenyl)pyridine-2(1*H*)-one (4.20mmol, 0.85g), 2-chloro-5-(chloromethyl)pyridine (1.5eq, 6.30mmol, 1.02g), K₂CO₃ (2eq, 8.40mmol, 1.17g) in THF (10mL) were heated at 70°C for 2 hours. Then, the reaction was cooled to room temperature. The suspension was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by short open column chromatography CH₂Cl₂/MeOH(NH₃)sat. 1% yielding 1-((6-chloropyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one as white solid (1.04g, 75%)

*Step 2 : 1-((6-Iodopyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one*

According to Scheme 33 Step 1: 1-((6-Chloropyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (2.54mmol, 0.83g), trimethylsilyl chloride (3.3mmol, 0.42mL) and NaI (7.60mmol, 1.14g) in propionitrile (20mL) were heated at 140°C for 20 minutes under microwave irradiation conditions. Then the suspension was filtered off and the solid obtained was partitioned between CH₂Cl₂/water. The aqueous layer was extracted several times with CH₂Cl₂; the organic layers were combined, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was treated with Et₂O giving an 1-((6-iodopyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (600mg, 61%) as a pale grey solid.

Step 3 : 5-(4-Methoxyphenyl)-1-((6-(2-(trimethylsilyl)ethynyl)pyridin-3-yl)methyl)pyridin-2(1H)-one

According to Scheme 33 Step 2: A mixture of 1-((6-iodopyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (0.48mmol, 200mg), PdCl₂(PPh₃)₂ (33μmol, 23mg),
5 CuI (24μmol, 4.5mg), ⁱPr₂EtN (0.99mmol, 1.72μl), trimethylsilylacetylene (1.43mmol, 203μL) and DMF (3 mL, previously deoxygenated) was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge CH₂Cl₂/MeOH(NH₃)sat. 3%
10 yielding 5-(4-methoxyphenyl)-1-((6-(2-(trimethylsilyl)ethynyl)pyridin-3-yl)methyl)pyridin-2(1H)-one (174mg, 93%).

Step 4 : 1-((6-Ethynylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

A mixture of 5-(4-methoxyphenyl)-1-((6-(2-(trimethylsilyl)ethynyl)pyridin-3-yl)methyl)pyridin-2(1H)-one (0.60mmol, 240mg), tetrabutylammonium fluoride (1.20mmol, 1.2mL) in THF (5mL) and H₂O (1mL) was stirred at room temperature for
15 2 hours. The solvent was evaporated under reduced pressure. The residue was taken up in CH₂Cl₂, was washed with water, dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge CH₂Cl₂/MeOH(NH₃)sat. 3%. The fractions were collected and evaporated. The residue
20 thus obtained was triturated with diisopropyl ether. The precipitated solid was filtered off and dried. Further purification by circular chromatography-TLC CH₂Cl₂/MeOH(NH₃)sat. 3% yielding 1-((6-ethynylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (68mg, 35%).
25 M.p.: 273°C; ¹H NMR (400 MHz, CDCl₃) δ8.61 (d, 1H, *J*=2.1 Hz); 7.72 (dd, 1H, *J*=8.1, 2.1 Hz); 7.60 (dd, 1H, *J*=9.4, 2.6 Hz); 7.46 (d, 1H, *J*=8.1 Hz); 7.40 (d, 1H, *J*=2.7 Hz); 7.28 (d, 2H, *J*=8.5 Hz); 6.94 (d, 2H, *J*=8.7 Hz); 6.64 (d, 2H, *J*=8.7 Hz); 7.28 (d, 2H, *J*=8.5 Hz); 6.94 (d, 2H, *J*=8.7 Hz); 6.70 (d, 1H, *J*=9.5 Hz); 5.21 (s, 2H); 3.83 (s, 3H); 3.16 (s, 1H).

Step 5 : 1-((6-Ethylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one

According to Scheme 33 Step 3: To a suspension of Pd/C 10% (0.05 eq) in MeOH (10mL) under N₂ atmosphere, a solution of 1-((6-ethynylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (0.15mmol, 48mg) was added at room temperature.

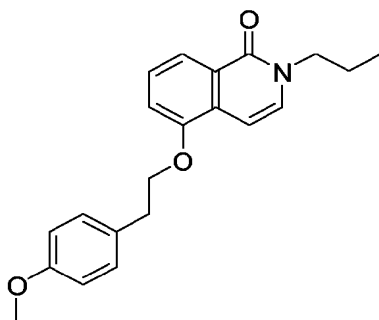
5 The flask was evacuated and filled with hydrogen until the pressure reached 20 psi. The resulting suspension was shaken at room temperature for 1 hour. The catalyst was filtered off and the filtrate was evaporated under vacuum to give a residue. The residue was purified in a circular chromatography-TLC CH₂Cl₂/MeOH(NH₃)sat. 2% yielding 1-((6-ethylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one (30mg, 61%).

10 M.p.: 130°C; LC (ACE Column): RT = 3.55min; MS *m/z* (CI) [MH]⁺ = 321; ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, 1H, *J*=2.1 Hz); 7.66 (dd, 1H, *J*=8.0, 2.4 Hz); 7.58 (dd, 1H, *J*=9.5, 2.7 Hz); 7.42 (d, 1H, *J*=2.3 Hz); 7.25-7.30 (m, 2H); 7.15 (d, 1H, *J*=7.9 Hz); 6.90-6.95 (m, 2 H); 6.69 (d, 1H, *J*=9.5 Hz); 5.18 (s, 2H); 3.83 (s, 3H); 2.81 (q, 2H, *J*=7.7 Hz); 1.29 (t, 3H, *J*=7.6 Hz).

15

EXAMPLE 53 : 5-(4-Methoxyphenethoxy)-2-propylisoquinolin-1(2H)-one (Final Compound 13-06)

20



Step 1 : 5-Chloroisoquinoline-N-oxide

According to Scheme 34 Step 1: The title compound was prepared from isoquinolin-5-ol (1eq, 6.89mmol, 1.00g) according to the procedure described for Example 38 Step 1.

25 The crude residue was recrystallized in CH₂Cl₂ to yield 5-chloroisoquinoline-N-oxide (6.58mmol, 1.06g, 96%) as a beige solid.

Step 2 : 5-(4-Methoxyphenethoxy)isoquinoline-N-oxide

According to Scheme 34 Step 2: The title compound was prepared from 5-chloroisoquinoline-N-oxide (1eq, 6.21mmol, 1.00g) and 1-(2-chloroethyl)-4-methoxybenzene (2eq, 12.4mmol, 2.12g) according to the procedure described for

5 Example 1 Step 2. Reaction conditions: microwaved at 180°C for 15 min in acetonitrile. The crude product was purified by silica gel chromatography (AIT Flashsmart preppacked column 70g SiO₂) using cyclohexane/AcOEt 85/15 to 50/50 and MeOH to afford 5-(4-methoxyphenethoxy)isoquinoline-N-oxide (2.73mmol, 0.81g, 44%).

10 LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.98min; MS *m/z* (CI) [MH]⁺= 296.

Step 3 : 5-(4-Methoxyphenethoxy)isoquinolin-1(2H)-one

According to Scheme 34 Step 3: The title compound was prepared from 5-(4-methoxyphenethoxy)isoquinoline-N-oxide (1eq, 2.73mmol, 0.81g) according to the

15 procedure described for Example 38 Step 2. The crude product was used without being purified and yielded 5-(4-methoxyphenethoxy)isoquinolin-1(2H)-one (1.08mmol, 0.32g, 40%) as a brown solid.

Step 4 : 5-(4-Methoxyphenethoxy)-2-propylisoquinolin-1(2H)-one

According to Scheme 34 Step 4: The title compound was prepared from 5-(4-methoxyphenethoxy)isoquinolin-1(2H)-one (1eq, 0.34mmol, 0.10g) and 1-bromopropyl (1.5eq, 0.51mmol, 46μL) according to the procedure described for Example 1 Step 2. Reaction conditions: microwaved at 180°C for 15 min. in acetonitrile. The crude

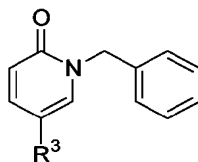
25 product was purified by flash chromatography over silica gel (AIT Flashsmart preppacked column 25g SiO₂) using pure CH₂Cl₂/MeOH 100/0 to 99/1 to afford 5-(4-methoxyphenethoxy)-2-propylisoquinolin-1(2H)-one (59μmol, 20mg, 17%) as an orange oil.

LC (XTerra RP₁₈, 3.5μm, 3.0x50mm Column): RT = 4.84min; MS *m/z* (CI) [MH]⁺=

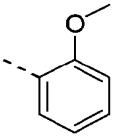
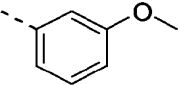
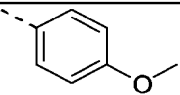
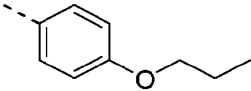
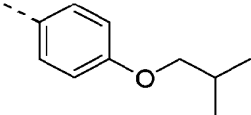
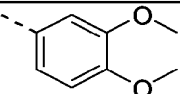
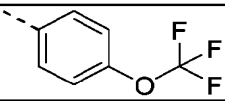
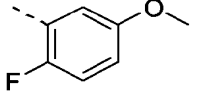
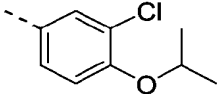
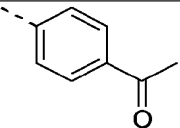
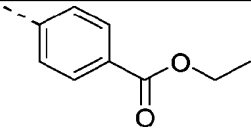
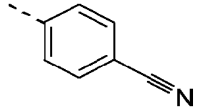
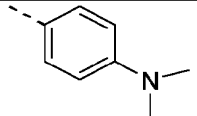
30 338; ¹H NMR (300MHz, CDCl₃) δ 0.90 (t, J=7.7Hz, 3H), 1.74 (q, J=8.5Hz, 2H), 3.06 (t, J=6.6Hz, 2H), 3.73 (s, 3H), 3.89 (t, J=7.4Hz, 2H), 4.17 (t, J=6.6Hz, 2H), 6.75-6.83

(m, 3H), 6.98 (t, J=7.2Hz, 2H), 7.18 (d, J=8.2Hz, 2H), 7.29 (t, J=8.2Hz, 1H), 7.92 (d, J=8.2Hz, 1H).

- 5 The compounds in the following Tables have been synthesized according to the previous examples, as denoted in the column denoted as "Exp. Nr". The compound denoted with the asterisk has been exemplified in the Examples. When it concerns the bivalent linkers V₁ and V₂, it is noted that the left part of the linkers V₁ and V₂ is attached to the pyridinyl-moiety.

Table 1

Co.nr.	Exp. nr.	R ³	
1-01	1		
1-02	2		
1-03	2		
1-04	7		
1-05	2		
1-06	2		
1-07	2		
1-08	1		
1-09	2		
1-10	2		
1-11	1		
1-12	2		
1-13	20		

Co.nr.	Exp. nr.	R ³	
1-14	2		
1-15	2		
1-16	1		
1-17	2		
1-18	20		
1-19	2		
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1-21	2		
1-22	2		
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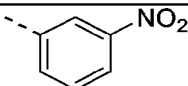
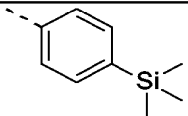
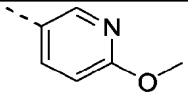
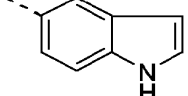
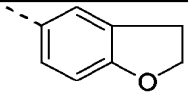
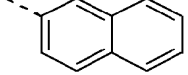
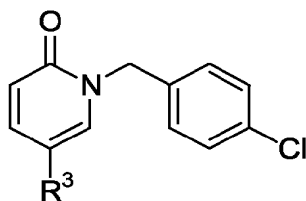
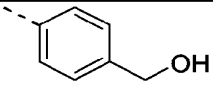
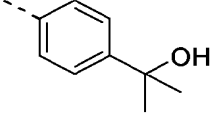
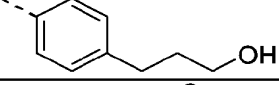
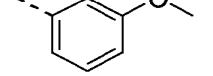
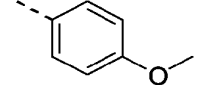
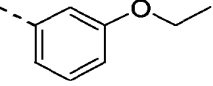
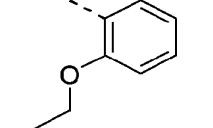
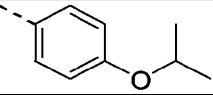
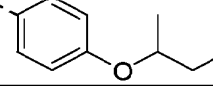
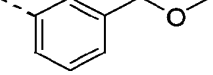
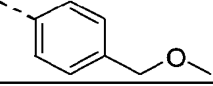
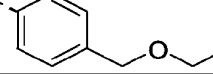
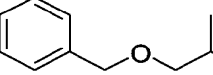
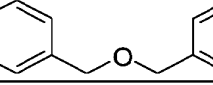
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1-27	2		
1-28	2		
1-29	1		
1-30	2		
1-31	2		
1-32	2		

Table 2

Co.nr.	Exp. nr.	R ³	
2-01	36*		
2-02	2		
2-03	2		
2-04	1		
2-05	1		
2-06	1		
2-07	2		
2-08	2		
2-09	2		
2-10	2		
2-11	2		
2-12	20		
2-13	20		

Co.nr.	Exp. nr.	R ³	
2-14	35		
2-15	30*		
2-16	2*		
2-17	1		
2-18	2		
2-19	1		
2-20	2		
2-21	20		
2-22	20		
2-23	2		
2-24	2		
2-25	35*		
2-26	47		
2-27	35		
2-28	47	